Docket No. 61071-AZ/JPW/GJG/ACK

Application
for
United States Letters Patent

To all whom it may concern:

Be it known that

Samuel J. Danishefsky and Bishan Zhou

have invented certain new and useful improvements in

COMPOUNDS OF THE SAFRAMYCIN-ECTEINASCIDIN SERIES, USES, AND SYNTHESIS THEREOF

of which the following is a full, clear and exact description.

COMPOUNDS OF THE SAFRAMYCIN-ECTEINASCIDIN SERIES, USES, AND SYNTHESIS THEREOF

This application is a divisional of U.S. Serial No. 09/765,515, filed January 19, 2001, now allowed, which claims the benefit of U.S. Provisional Application No. 60/177,071, filed January 19, 2000, the contents of all of which are hereby incorporated by reference.

This invention has been made with government support under National Institutes of Health Grant Nos. CA-28824 and HL-25848. Accordingly, the U.S. Government may have certain rights in the invention.

Throughout this application, various publications may be referenced by Arabic numerals in brackets. Full citations for these publications may be found at the end of the specification immediately preceding the claims. The disclosures of these publications in their entireties are hereby incorporated by reference into this application in order to more fully describe the state of the art as known to those skilled therein as of the date of the invention described and claimed herein.

Field of Invention

The disclosed invention relates to novel compounds of the saframycin-ecteinascidin series having cytotoxic properties and to schemes for the total synthesis of such compounds.

Background of the Invention

The screening of natural product sources for new drug candidates with useful therapeutic margins has led to a variety of novel structures. One of the most fascinating and promising of these is ecteinascidin 743 (ET 743) derived from the marine tunicate *Ecteinascidia turbinata*.(1) The novel structure of Et 743, its difficult availability, and its exceedingly potent cytotoxicity render it an attractive target for total synthesis. This goal was undertaken and accomplished in a most interesting fashion

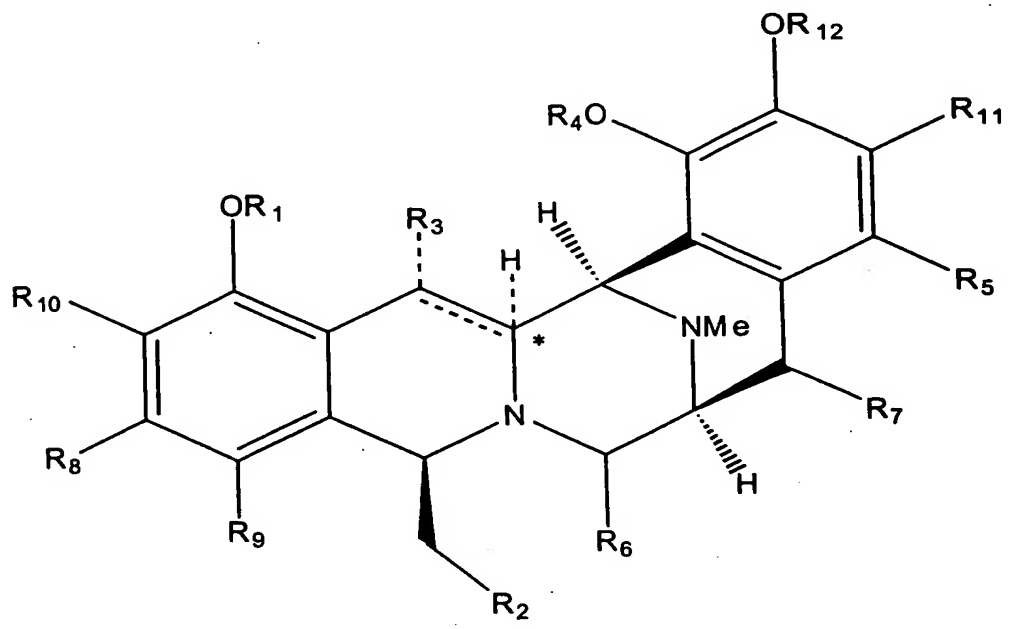
by E. J. Corey and coworkers.(2) Follow-up studies by Corey, Schreiber (3) and co-workers resulted in the demonstration that a significantly simplified version of ET 743 (ie: phthalascidin) retains the cytotoxicity of the natural product. Previously, well before the ecteinascidins were known, some of the named inventors had accomplished what was then the only total synthesis of quinocarcinol.(4) The central Mannich-like envelopment strategy, learned from work in the quinocarcin series, was adapted to the ET problem.

While ET 743 was previously known, the total synthesis of ET 743 was first accomplished by Corey in 1996 and, prior to this invention, was the only total synthesis of an ecteinascidin.

It is known that saframycin B, saframycin A (13,14), saframycin S (15), ecteinascidin 729 (Et 729)(16), Et 743 and Phthalascidin (3) all posses cytotoxic antitumor and antibiotic characteristics. It is also known that saframycin S, saframycin B, saframycin A, Et 729, Et 743 (17), and phthalascidin (3) all possess a two tetrahydroisoquinoline aromatic carbon nitrogen framework. Saframycins and ecteinascidins have been shown to interact with DNA. Interactions are believed to occur between DNA and the tetrahydroisoquinoline aromatic carbon nitrogen framework. (2,18)

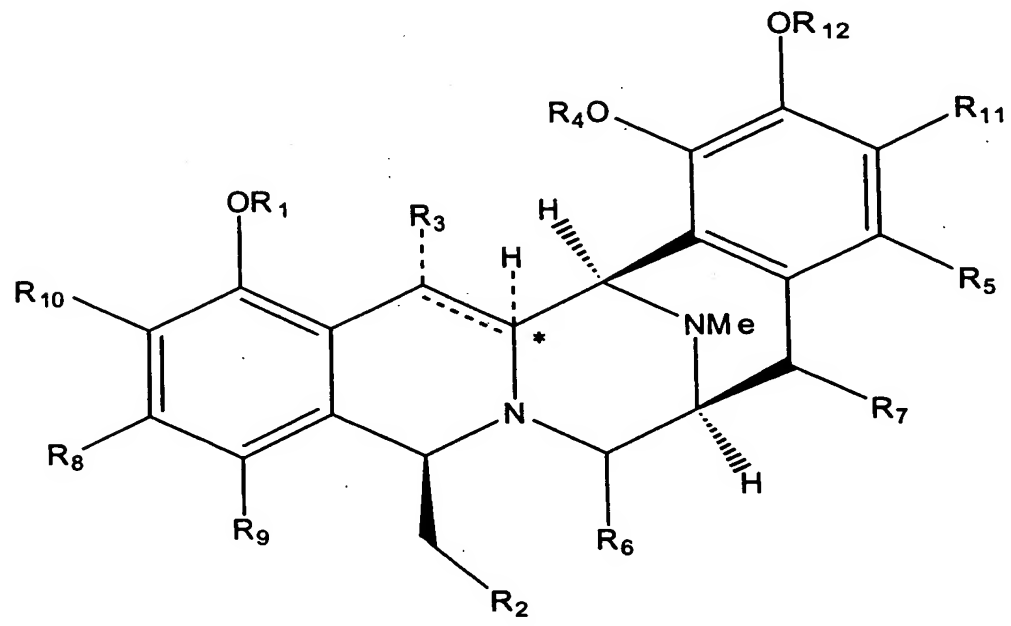
Summary of the Invention

The subject invention provides compounds of the saframycin-ecteinascidin series with cytotoxic properties having the following general formula, their uses and synthesis:



wherein R_1 and R_4 is H, a C_1 to C_4 alkyl group, or an acyl group; wherein R_2 is an ether, ester, amide, a phthalimide group, a substituted phthalimide group or is covalently bound to R_6; wherein R_3 is =O, OH, an ether group, an acyl group such as OC(O)Me, OC(O)Bn and OC(O)Et, or a sulfide group; wherein R_5 is H, halogen, OH, an ether group, an acyl group, or an amide group; wherein R_6 is =O, OH, OCH_3, CN, or an acyloxy group or is covalently bound to R_2; wherein R_7, is =O, OH, halogen, an ether group, or an acyl group; wherein R_8 and R_9 are independently H, CH_3, OCH_3, OC_2H_5, CF_3, halogen such as Br and F, or R_8 and R_9 are joined together as a methylenedioxy group, or other five or six membered ring; wherein R_{10} and R_{11} are independently CH_3, OCH_3, OC_2H_5, SCH_3, or SC_2H_5; wherein R_{12} is H, a C_1 to C_4 alkyl group, or an acyl group; and wherein the chiral center marked * has the R or the S configuration.

The subject invention also provides for a group of saframycin-ecteinascidin series compounds with cytotoxic properties having the following general formula, their uses and synthesis:



wherein R_1 and R_4 is H, a C_1 to C_4 alkyl group, or an acyl group; wherein R_2 is an ether, ester, amide, an aromatic group or is covalently bound to R_6; ; wherein R_3 is =O, OH, an ether group, an acyl group such as OC(O)Me, OC(O)Bn and OC(O)Et, a sulfide group or H; wherein R_5 is H, halogen, OH, an ether group, an acyl group, or an amide group; wherein R_6 is =O, OH, OCH_3, CN, or an acyloxy group or is covalently bound to R_2; wherein R_7, is =O, OH, halogen, an ether group, or an acyl group; wherein R_8 and R_9 are independently H, CH_3, OCH_3, OC_2H_5, CF_3, halogen such as Br and F, or R_8 and R_9 are joined together as a methylenedioxy group, or other five or six membered ring; wherein R_{10} and R_{11} are independently CH_3, OCH_3, OC_2H_5, SCH_3, or SC_2H_5; wherein R_{12} is H, a C_1 to C_4 alkyl group, or an acyl group; and wherein the chiral center marked * has the R or the S configuration.

Description of the Figures

Figure 1 shows the structures of Saframycin B and Ecteinascidin 743.

Figure 2 is a Table showing the cytotoxicity, antimetabolism and antimicrobial activity of ET 743.

Figure 3 shows the mechanism for the catalytic activation of ET 743 and alkylation of 6GN2.

Figures 4A, 4B and 4C show the retrosynthesis analysis of ET 743 and Saframycin B.

Figures 5A and 5B show the enantioselective synthesis of amino acid for the synthesis strategy A of Saframycin B.

Figure 6 shows the enantioselective synthesis of tertahydroisoquinoline, which is used as a subunit in the foregoing synthesis.

Figures 7A and 7B show the coupling strategy for the synthesis strategy A of Saframycin B.

Figures 8A and 8B show the modified synthesis of amino acid for synthesis strategy B of Saframycin B.

Figures 9A and 9B show the synthesis of the pentasubstituted aromatic system and the tertahydroisoquinoline of ET 743, i.e. the left part of ET 743.

Figure 10A shows the coupling steps for the synthesis strategy B for Saframycin B.

Figur 10B shows the cyclization for the synthesis strategy B of Saframycin B.

Figure 11 shows the final steps for the total synthesis of Saframycin B.

Figure 12 shows the enantioselective synthesis of amino acid for the synthesis of ET 743.

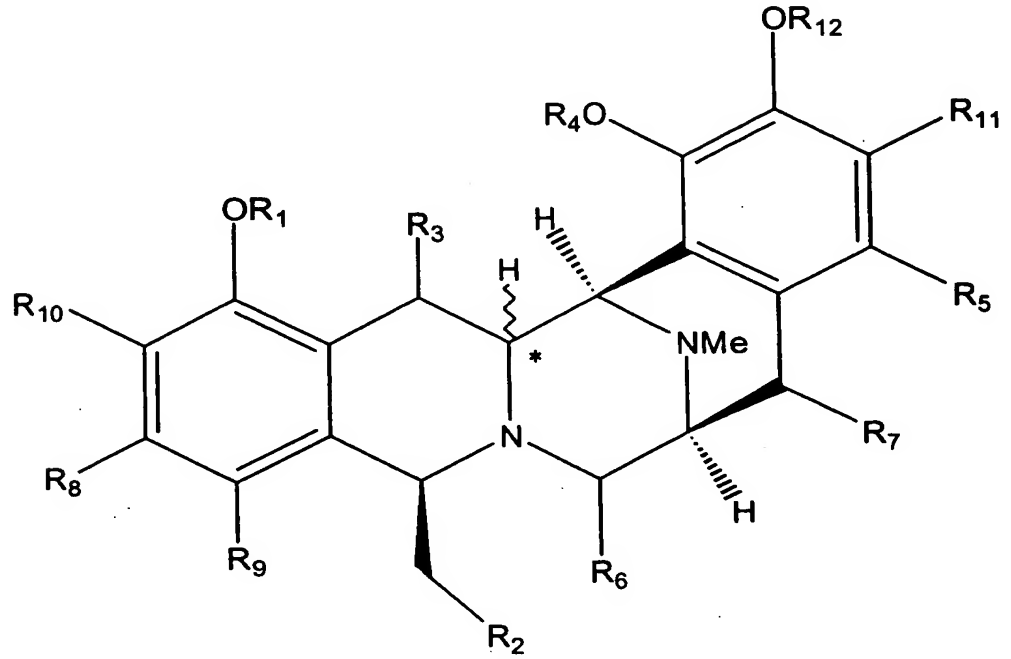
Figure 13 shows the coupling and the cyclization steps in synthesis for ET 743.

Figure 14 shows the ET 743 series cyclization analogs.

Figure 15 shows the plan for the total synthesis of ET 743.

Detailed Description of the Invention

An embodiment of the subject invention provides compounds having the formula:



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wherein R_1 and R_4 is H, a C_1 to C_4 alkyl group, or an acyl group;

wherein R_2 is an ether, ester, amide, a phthalimide group, a substituted phathalimide group or is covalently bound to R_6;

wherein R_3 is =O, OH, an ether group, an acyl group, or a sulfide group;

wherein R_5 is H, halogen, OH, an ether group, an acyl group, or an amide group;

wherein R_6 is =O, OH, OCH_3, CN, an acyloxy group or is covalently bound to R_2; ;

wherein R_7, is =O, OH, halogen, an ether group, or an acyl group;

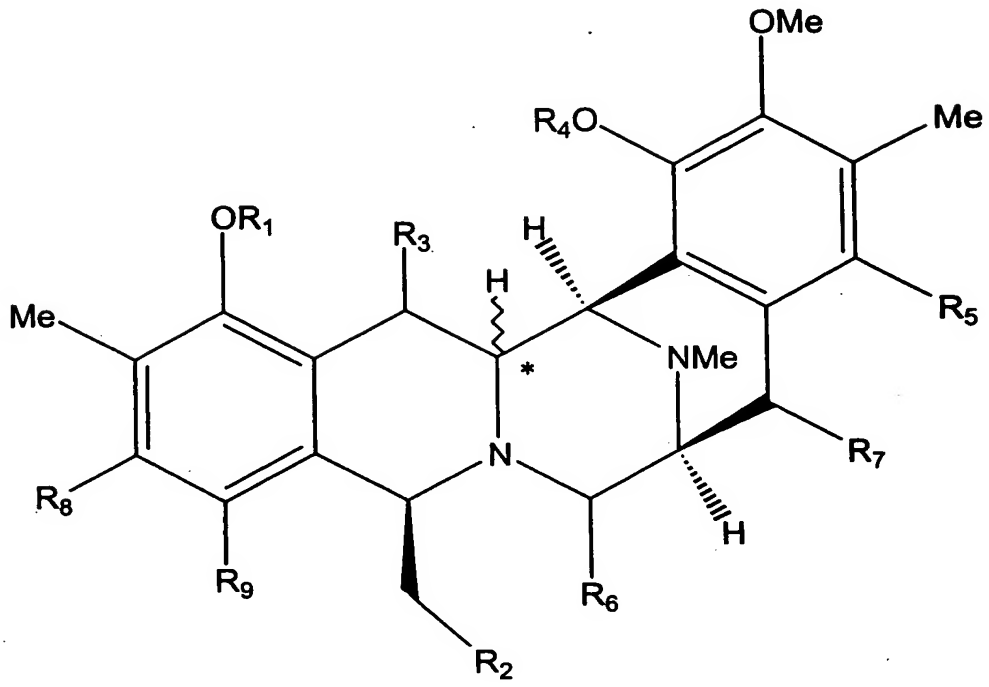
wherein R_8 and R_9 are independently H, CH_3, OCH_3, OC_2H_5, Br, F, CF_3, or R_8 and R_9 are joined together as a methylenedioxy group, or other five or six membered ring;

wherein R_{10} and R_{11} are independently CH_3, OCH_3, OC_2H_5, SCH_3, or SC_2H_5;

wherein R_{12} is H, a C_1 to C_4 alkyl group, or an acyl group; and

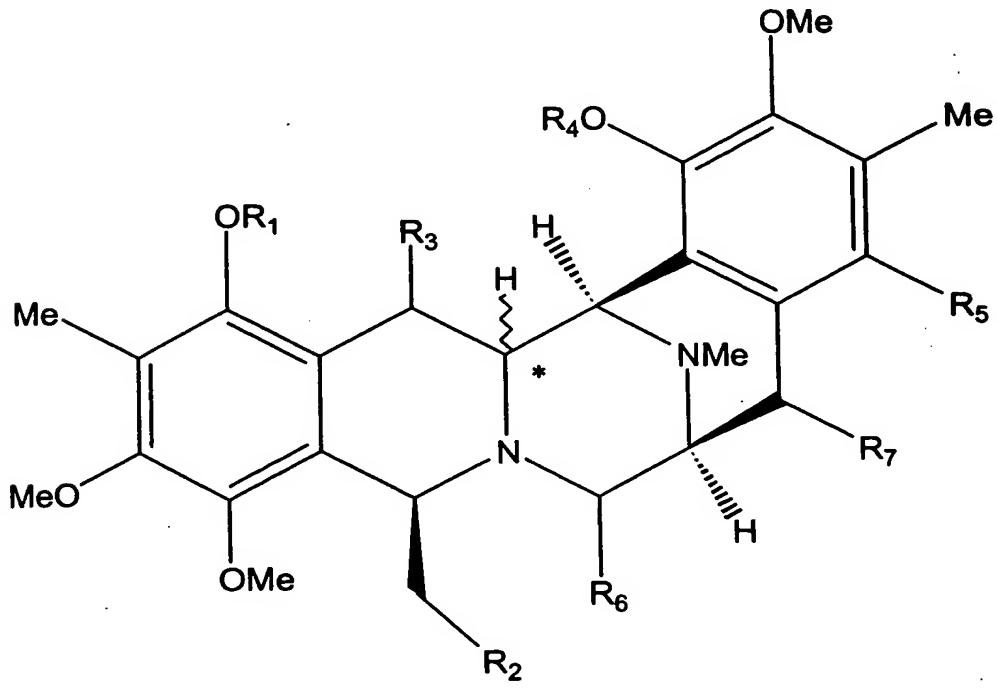
wherein the chiral center marked * has the R or the S configuration.

In another embodiment, the compound has the formula:



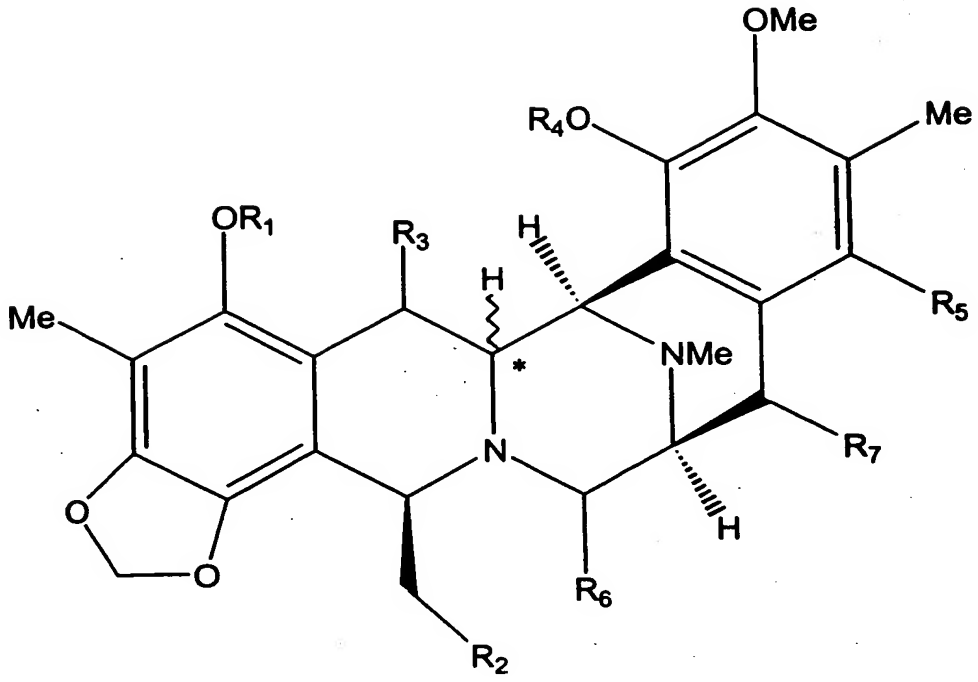
where R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, and R_9 are as defined above.

In yet another embodiment, the compound has the formula:



where R_1, R_2, R_3, R_4, R_5, R_6, and R_7 are as defined above.

In yet another embodiment, the compound has the formula:



where R_1, R_2, R_3, R_4, R_5, R_6, and R_7 are as defined above.

In preferred embodiments of the immediately preceding formula, R_1 is CH_3, R_3 is =O, R_4 is CH_3, R_5 is OCH_3, R_6 is =O, and R_7 is H.

In another preferred embodiment of the preceding formula, R_1 is H, R_3 is =O, R_4 is CH_3, R_5 is OCH_3, R_6 is =O, and R_7 is H.

In yet another preferred embodiment of the preceding formula, R_1 is H, R_3 is =O, R_4 is benzyl , R_5 is OCH_3, R_6 is =O, and R_7 is H.

In yet another preferred embodiment of the preceding formula, R_1 is H, R_3 is =O, R_4 is H, R_5 is OCH_3, R_6 is =O, and R_7 is H.

In yet another preferred embodiment of the preceding formula, R_1 is H, R_3 is =O, R_4 is H, R_5 is H, R_6 is =O, and R_7 is H.

In preferred embodiments of the immediately preceding formula, R_1 is CH_3, R_3 is =O, R_4 is CH_3, R_5 is OCH_3, R_6 is =O, and R_7 is H.

In another preferred embodiment of the preceding formula, R_1 is H, R_3 is =O, R_4 is CH_3, R_5 is OCH_3, R_6 is =O, and R_7 is H.

In yet another preferred embodiment of the preceding formula, R_1 is H, R_3 is =O, R_4 is benzyl , R_5 is OCH_3, R_6 is =O, and R_7 is H.

In yet another preferred embodiment of the preceding formula, R_1 is H, R_3 is =O, R_4 is H, R_5 is OCH_3, R_6 is =O, and R_7 is H.

In yet another preferred embodiment of the preceding formula, R_1 is H, R_3 is =O, R_4 is H, R_5 is H, R_6 is =O, and R_7 is H.

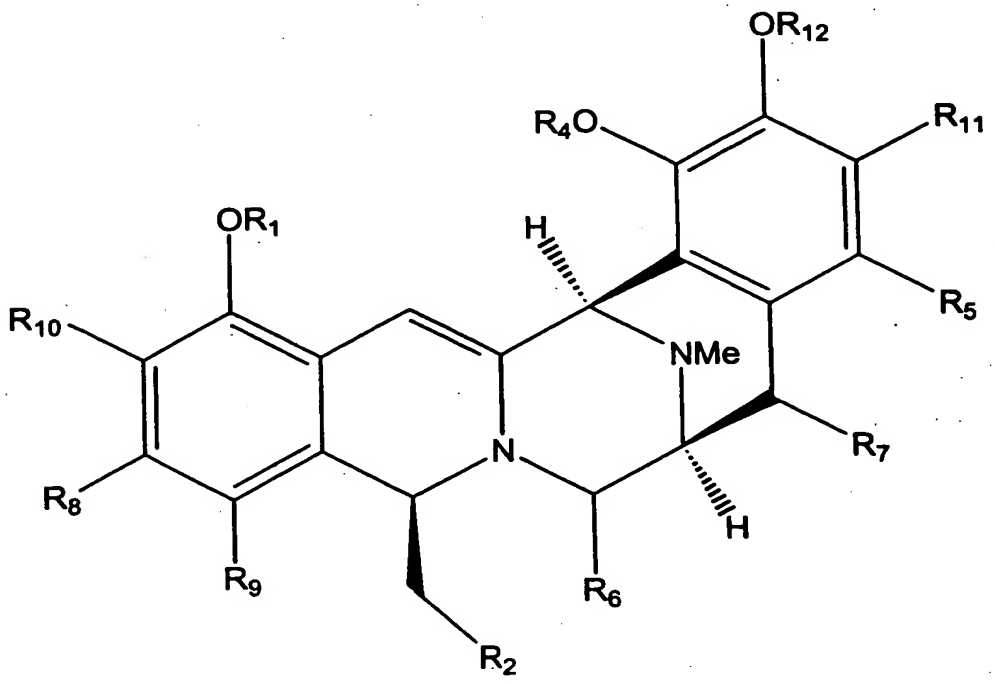
In yet another preferred embodiment of the preceding formula, R_1 is H, R_3 is =O, R_4 is H, R_5 is halogen, R_6 is =O, and R_7 is H.

In all of the embodiments, and particularly in the preferred embodiments, R_2 is OC(O)H, R_2 is H, R_2 is OH, R_2 is -O-benzyl , R_2 is $OCOCH_3$, R_2 is -O-*t*-butyldimethylsilyl, or R_2 is -O-Pivaloyl.

In yet another preferred embodiment of the preceding formula, R_1 is H, R_3 is =O, R_4 is H, R_5 is halogen, R_6 is =O, and R_7 is H.

In all of the embodiments, and particularly in the preferred embodiments, R_2 is OC(O)H, R_2 is H, R_2 is OH, R_2 is -O-benzyl , R_2 is $OCOCH_3$, R_2 is -O-*t*-butyldimethylsilyl, or R_2 is -O-Pivaloyl.

The subject invention also provides compounds having the formula:



wherein R_1 and R_4 is H, a C_1 to C_4 alkyl group, or an acyl group;

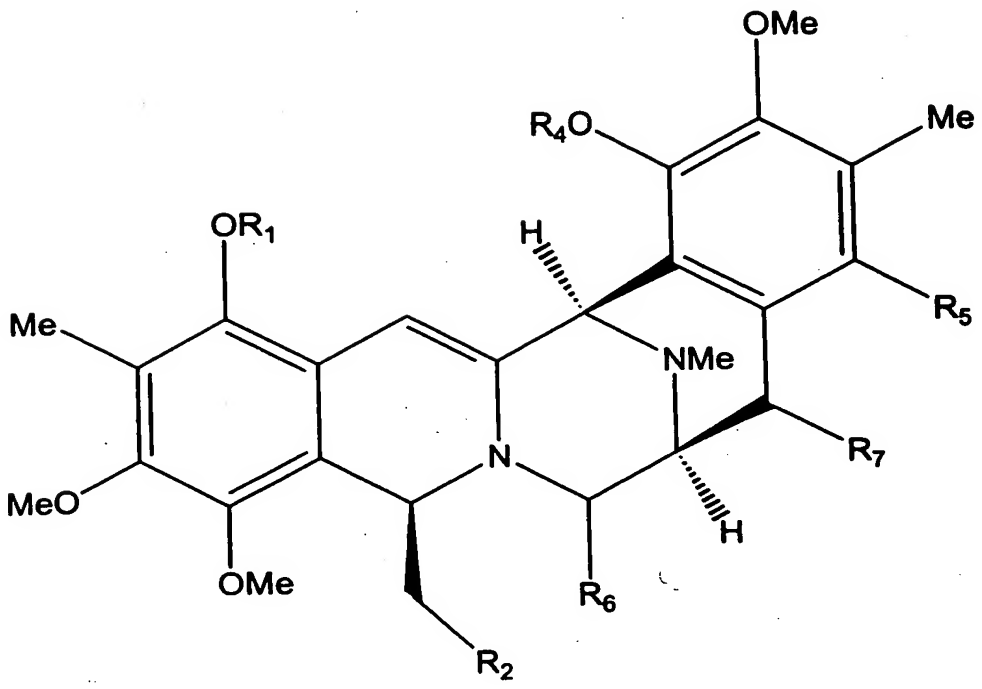
wherein R_2 is an ether, ester, amide, or a phthalimide group;

wherein R_5 is H, halogen, OH, an ether group, an acyl group, or an amide group;

wherein R_6 is =O, OH, OCH_3, CN, or an acyloxy group;

wherein R_7, is =O, OH, halogen, an ether group, or an acyl

In a preferred embodiment, the compound has the formula:



where R_1, R_2, R_4, R_5, R_6, and R_7 are as defined above.

In preferred embodiments of the immediately preceding formula, R_1 is CH_3, R_4 is CH_3, R_5 is OCH_3, R_6 is =O, and R_7 is H.

In another preferred embodiment of the preceding formula, R_1 is H, R_4 is CH_3, R_5 is OCH_3, R_6 is =O, and R_7 is H.

In yet another preferred embodiment of the preceding formula, R_1 is H, R_4 is benzyl , R_5 is OCH_3, R_6 is =O, and R_7 is H.

In yet another preferred embodiment of the preceding formula, R_1 is H, R_4 is H, R_5 is OCH_3, R_6 is =O, and R_7 is H.

In yet another preferred embodiment of the preceding formula, R_1 is H, R_4 is H, R_5 is H, R_6 is =O, and R_7 is H.

In yet another preferred embodiment of the preceding formula,

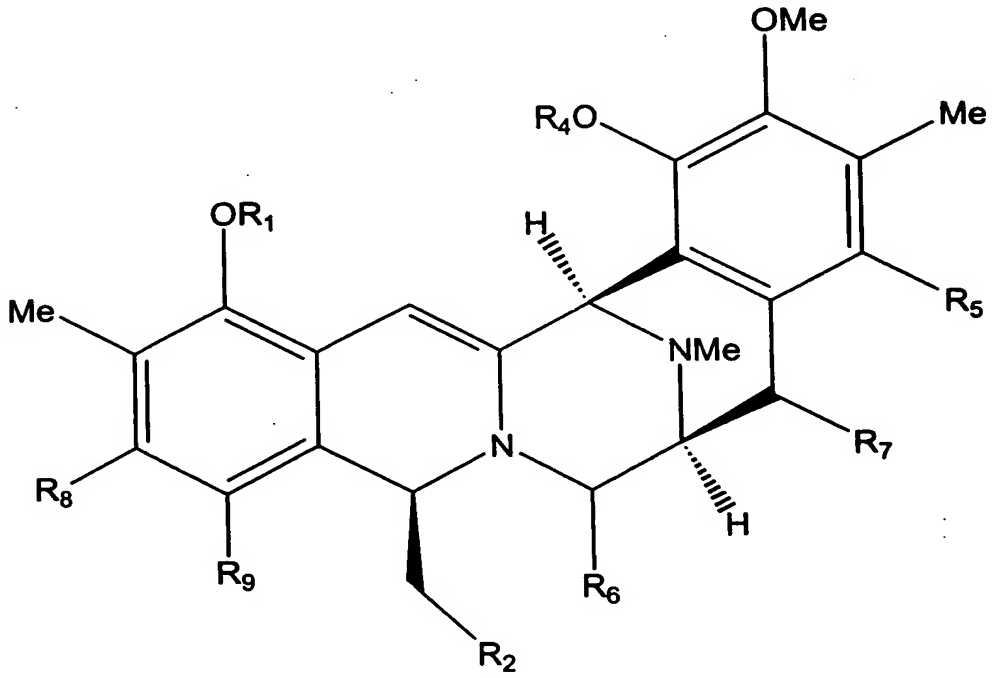
group;

wherein R_8 and R_9 are independently H, CH_3, OCH_3, OC_2H_5, Br, F, CF_3, or R_8 and R_9 are joined together as a methylenedioxy group, or other five or six membered ring;

wherein R_{10} and R_{11} are independently CH_3, OCH_3, OC_2H_5, SCH_3, or SC_2H_5;

wherein R_{12} is H, a C_1 to C_4 alkyl group, or an acyl group.

In another embodiment, the compound has the formula:

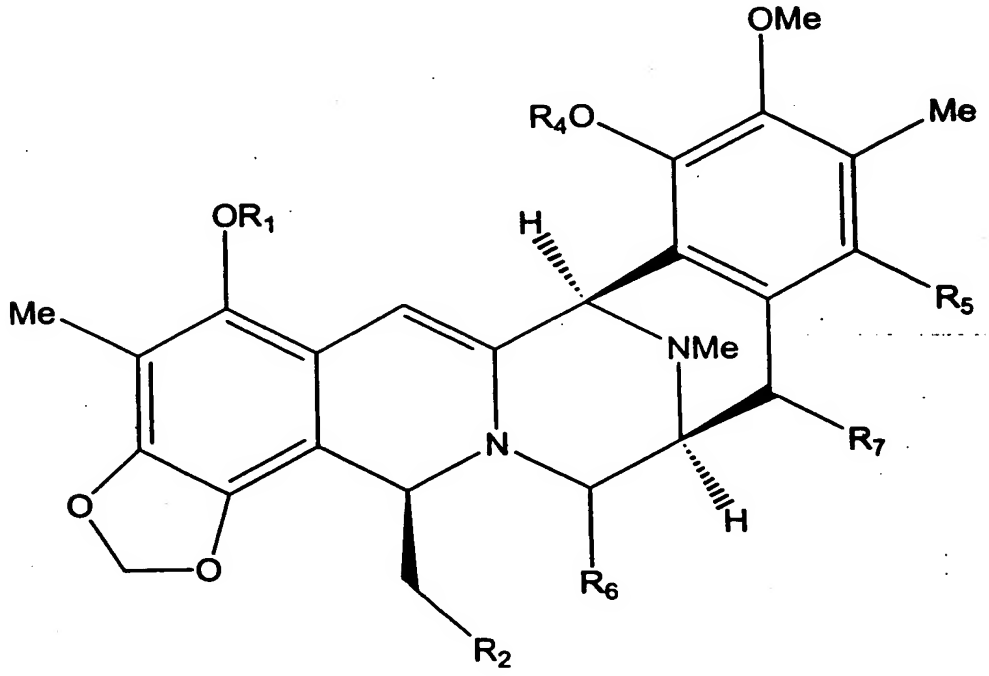


where R_1, R_2, R_4, R_5, R_6, R_7, R_8 and R_9 are as defined above.

R_1 is H, R_4 is H, R_5 is halogen, R_6 is =O, and R_7 is H.

In all of the embodiments, and particularly in the preferred embodiments, R_2 is OC(O)H, R_2 is H, R_2 is OH, R_2 is -O-benzyl , R_2 is $OCOCH_3$, R_2 is -O-*t*-butyldimethylsilyl, or R_2 is -O-Pivaloyl.

In another preferred embodiment, the compound has the formula:



where R_1, R_2, R_4, R_5, R_6, and R_7 are as defined above.

In preferred embodiments of the immediately preceding formula, R_1 is CH_3, R_4 is CH_3, R_5 is OCH_3, R_6 is =O, and R_7 is H.

In another preferred embodiment of the preceding formula, R_1 is H, R_4 is CH_3, R_5 is OCH_3, R_6 is =O, and R_7 is H.

In yet another preferred embodiment of the preceding formula, R_1 is H, R_4 is benzyl , R_5 is OCH_3, R_6 is =O, and R_7 is H.

In yet another preferred embodiment of the preceding formula, R_1 is H, R_4 is H, R_5 is OCH_3, R_6 is =O, and R_7 is H.

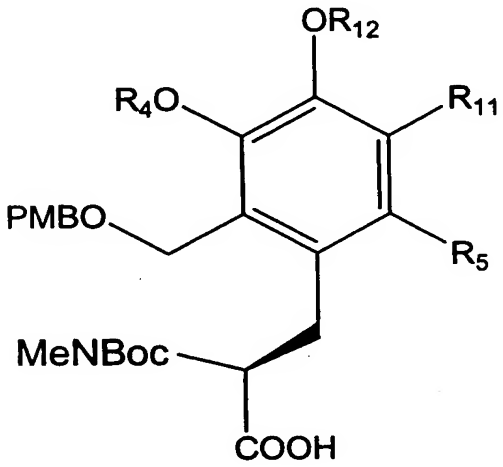
In yet another preferred embodiment of the preceding formula, R_1 is H, R_4 is H, R_5 is H, R_6 is =O, and R_7 is H.

In yet another preferred embodiment of the preceding formula, R_1 is H, R_4 is H, R_5 is halogen, R_6 is =O, and R_7 is H.

In yet another preferred embodiment of the preceding formula, R_1 is H, R_4 is CH_3, R_5 is CH_3, R_6 is =O, and R_7 is H (Compound **110**).

In all of the embodiments, and particularly in the preferred embodiments, R_2 is OC(O)H, R_2 is H, R_2 is OH, R_2 is -O-benzyl , R_2 is $OCOCH_3$, R_2 is -O-*t*-butyldimethylsilyl, or R_2 is -O-Pivaloyl.

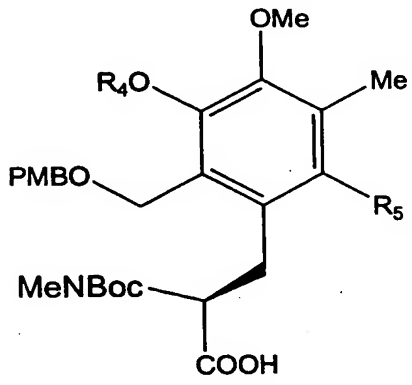
The subject invention also provides compounds having the following general formula which are used in the synthesis of compounds within the saframycin-ecteinascidin series:



A

wherein R_4 is H, a C_1 to C_4 alkyl group, or an acyl group;
wherein R_5 is H, halogen, OH, an ether group, an acyl group, a sulfide group or an amide group;
wherein R_{11} is CH_3, OCH_3, OC_2H_5, SCH_3, or SC_2H_5; and
wherein R_{12} is H, a C_1 to C_4 alkyl group, or an acyl group.

In another embodiment, the compound has the formula:

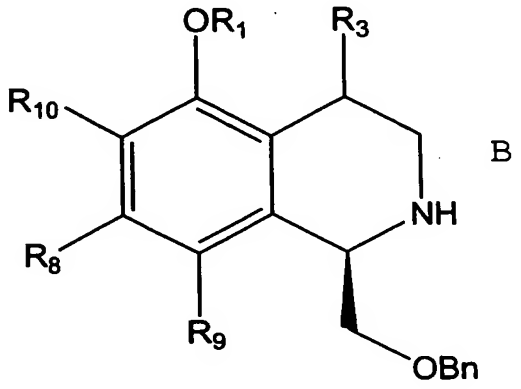


where R_4 and R_5 are defined as above.

In a preferred embodiment of the immediately preceding formula, R_4 is CH_3 and R_5 is CH_3 (compound **1**).

In another preferred embodiment of the preceding formula, R_4 is Benzene and R_5 is H (compound **3**).

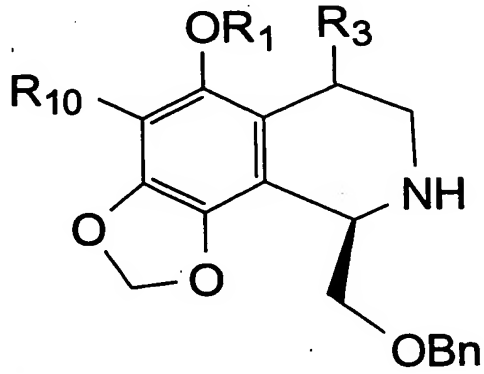
The subject invention also provides compounds having the following general formula which are used in the synthesis of compounds within the saframycin-ecteinascidin series:



B

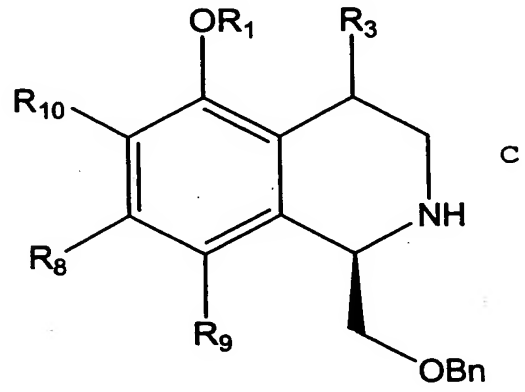
wherein R_1 is H, a C_1 to C_4 alkyl group, or an acyl group;
wherein R_3 is =O, OH, an ether group, an acyl group, a sulfide group or an amide group;
wherein R_8 and R_9 are independently H, CH_3, OCH_3, OC_2H_5, SCH_3, SC_2H_5, or R_8 and R_9 are joined together to form a five or six membered ring;
wherein R_{10} is CH_3, OCH_3, OC_2H_5, SCH_3, or SC_2H_5.

In another embodiment, of the immediately preceding formula the compound having the formula:



where R_1, R_3 and R_{10} are defined as above.

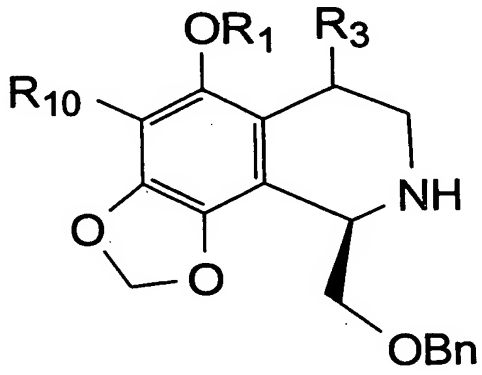
The subject invention also provides compounds having the following general formula which are used in the synthesis of compounds within the saframycin-ecteinascidin series:



C

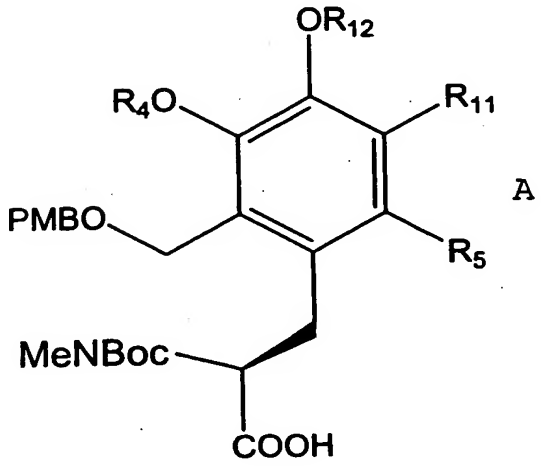
wherein R_1 is H, a C_1 to C_4 alkyl group, or an acyl group;
wherein R_3 is =O, OH, an ether group, an acyl group, a sulfide group, an amide group or H;
wherein R_8 and R_9 are independently H, CH_3, OCH_3, OC_2H_5, SCH_3, SC_2H_5, or R_8 and R_9 are joined together to form a five or six membered ring;
wherein R_{10} is CH_3, OCH_3, OC_2H_5, SCH_3, or SC_2H_5.

In another embodiment, of the immediately preceding formula the compound having the formula:



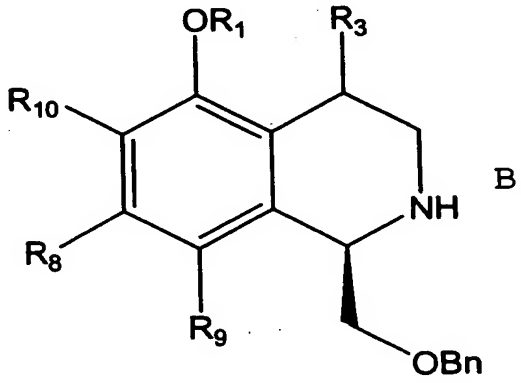
where R_1, R_3 and R_{10} are defined as above.

The subject invention also provides a method of producing the compounds within the saframycin-ecteinascidin series such as compound 1, which method comprises reacting a compound having the formula



A

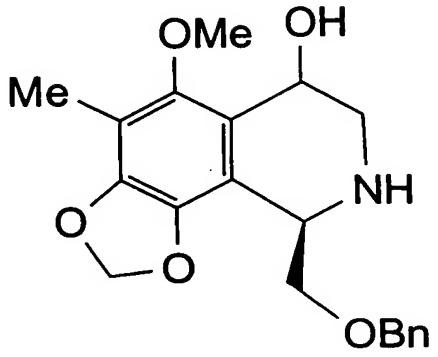
with a compound having the formula



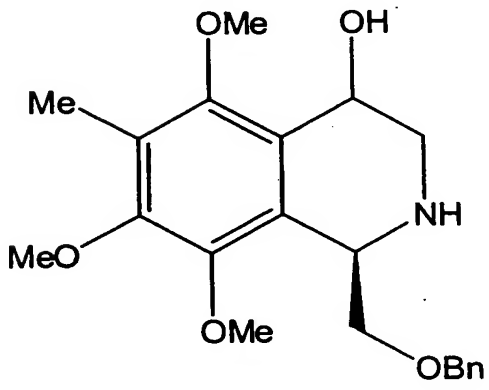
B

wherein R_1 and R_4 is H, a C_1 to C_4 alkyl group, or an acyl group;
wherein R_3 is =O, OH, an ether group, an acyl group, a sulfide group or an amide group;
wherein R_5 is H, halogen, OH, an ether group, an acyl group, or an amide group;
wherein R_8 and R_9 are independently H, CH_3, OCH_3, OC_2H_5, Br, F, CF_3, or R_8 and R_9 are joined together as a methylenedioxy group, or other five or six membered ring;

In yet another preferred embodiment, the compound has the formula:



In yet another preferred embodiment, the compound has the formula:



wherein R_{10} and R_{11} are independently CH_3, OCH_3, OC_2H_5, SCH_3, or SC_2H_5; and

wherein R_{12} is H, a C_1 to C_4 alkyl group, or an acyl group.

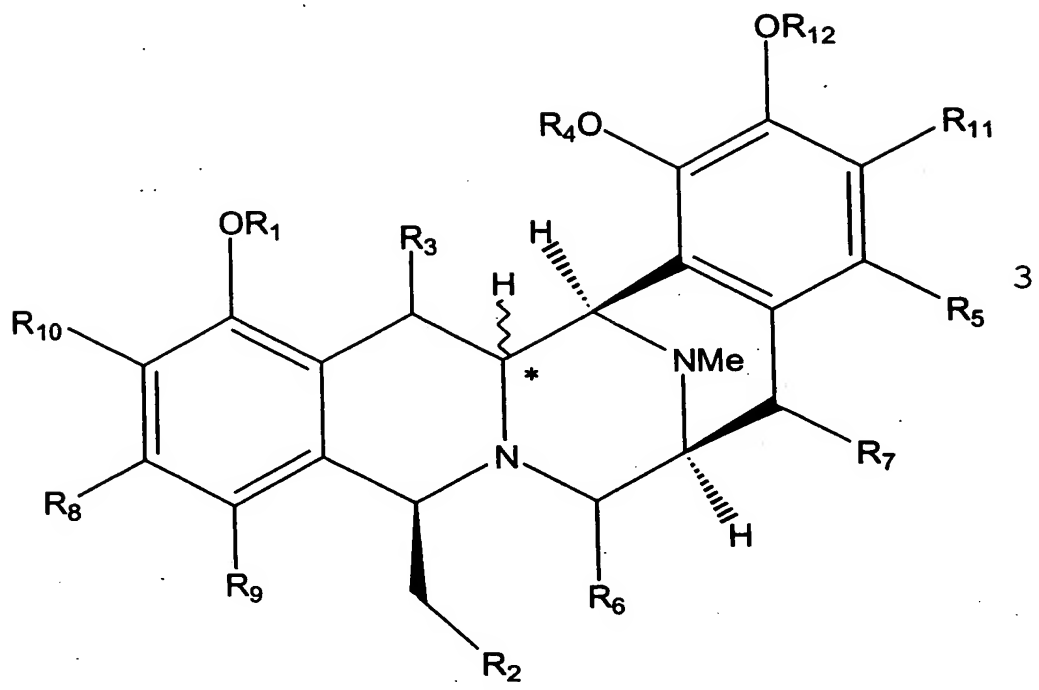
In an embodiment of the preceding method, the reaction is performed in the presence of *N,N*-bis(2-oxo-3-oxazolidinyl)phosphinic chloride.

In another embodiment of the method, the reaction is performed in the presence of Dess-Martin periodinane . In this embodiment, the reaction is further performed in the presence of CH_2Cl_2.

This invention also provides a method of producing the compound 2 above, which comprises reacting compound 1 above with camphor sulfonic acid (CSA) in the presence of toluene.

This invention also provides a method of producing the compound 1 above, which comprises reacting compound 2 above with H_2, 10%Pd/C, Ethanol-ascetic acid in the presence hydrochloric acid.

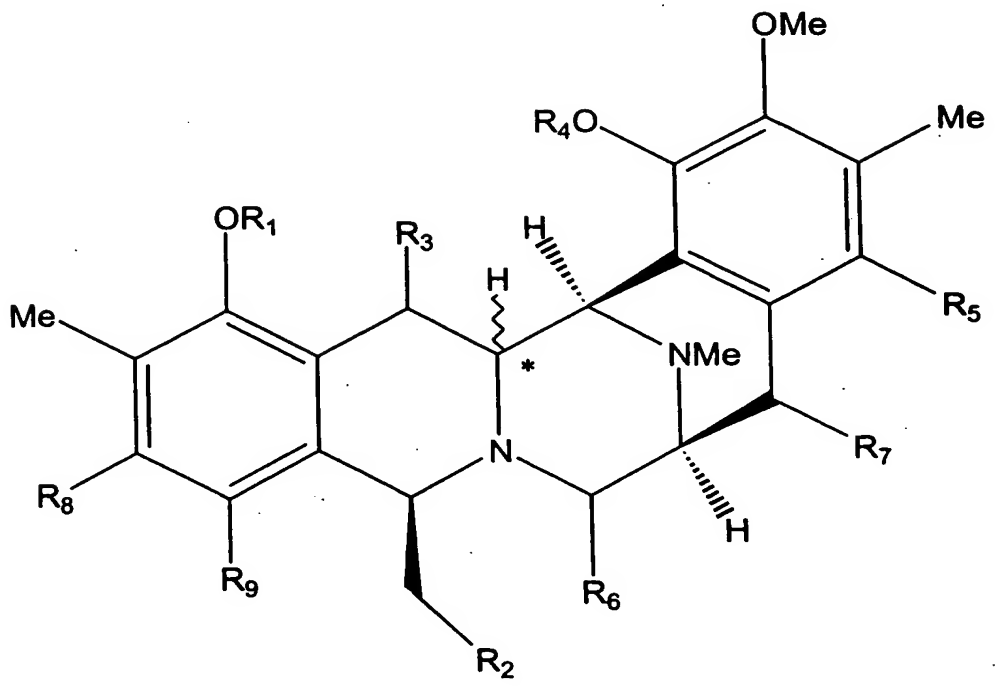
In another embodiment the subject invention provides for a compound having the formula:



wherein R_1 and R_4 is H, a C_1 to C_4 alkyl group, or an acyl group;
wherein R_2 is an ether, ester, amide, aromatic group or is covalently bound to R_6;
wherein R_3 is =O, OH, H, an ether group, an acyl group, or a sulfide group;
wherein R_5 is H, halogen, OH, $-OC_{(2-6)}$ alkyl group, an ether group, an acyl group, or an amide group;
wherein R_6 is =O, OH, OCH_3, CN, or an acyloxy group or is covalently bound to R_2;
wherein R_7, is H, =O, OH, OCH_3, halogen, an ether group, or an acyl group;
wherein R_8 and R_9 are independently H, CH_3, OCH_3, OC_2H_5, Br, F, CF_3, or R_8 and R_9 are joined together as a methylenedioxy group, or other five or six membered ring;
wherein R_{10} and R_{11} are independently CH_3, OCH_3, OC_2H_5, SCH_3, or SC_2H_5;

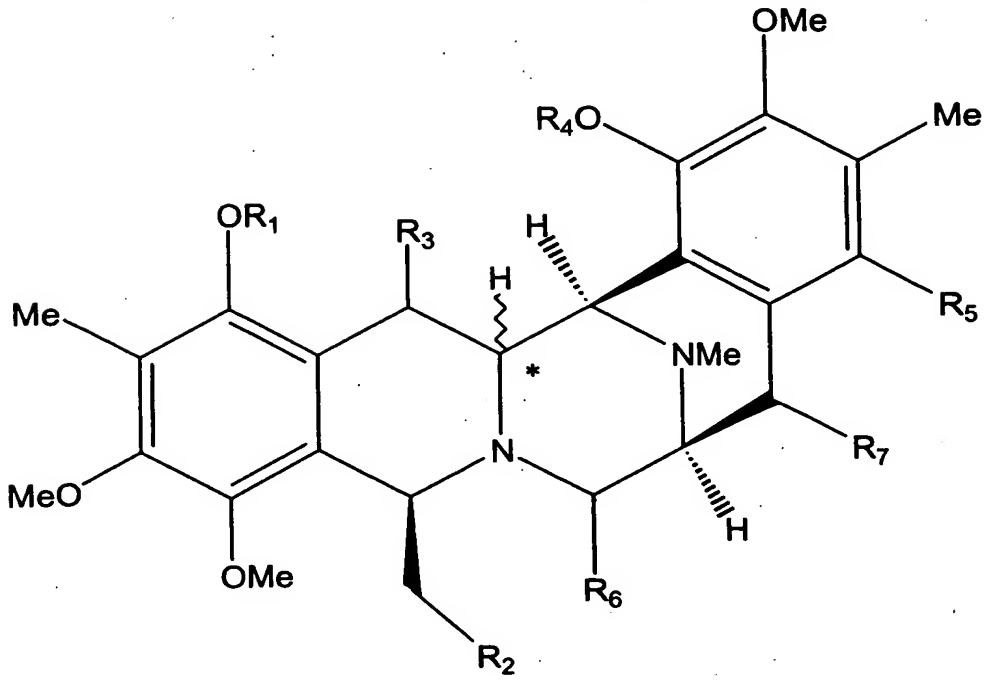
wherein R_{12} is H, a C_1 to C_4 alkyl group, or an acyl group; and wherein the chiral center marked * has the R or the S configuration.

In yet another embodiment the compound has the formula:



wherein R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, and R_9 are defined as in the preceding formula.

In yet another embodiment, the compound has the formula:



wherein R_1, R_2, R_3, R_4, R_5, R_6, and R_7 are defined as in the formula above.

In a preferred embodiment of the immediately preceding formula, R_1 is H, R_2 is OH, R_3 is H, R_4 is H, R_5 is H, R_6 is =O, and R_7 is H (Compound **113**).

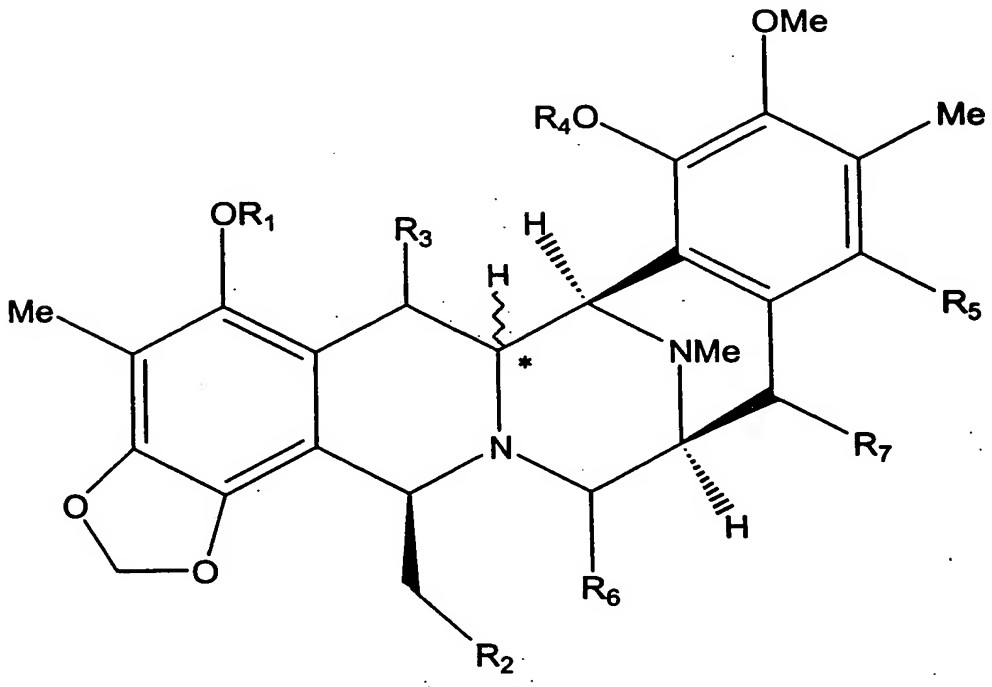
In another preferred embodiment of the preceding formula, R_1 is CH_3, R_2 is OH, R_3 is H, R_4 is CH_3, R_5 is OCH_3, R_6 is H and R_7 is H (Compound **107**).

In yet another preferred embodiment of the preceding formula, R_1 is H, R_2 is OH, R_3 is H, R_4 is CH_3, R_5 is OCH_3, R_6 is =O and R_7 is H (Compound **104**).

In yet another preferred embodiment of the preceding formula, R_1 is H, R_2 and R_6 are joined as an ester bond, R_3 is H, R_4 is CH_3, R_5 is OCH_3, and R_7 is H (Compound **105**).

In yet another preferred embodiment of the preceding formula, R_1 is CH_3 , R_2 and R_6 are joined as an ester bond, R_3 is H, R_4 is CH_3, R_5 is OCH_3, and R_7 is H (Compound **106**).

In another embodiment, the compound has the formula:



wherein R_1, R_2, R_3, R_4, R_5, R_6, and R_7 are defined as in the preceding formula.

In a preferred embodiment of the immediately preceding formula, R_1 is H, R_2 is OH, R_3 is OH, R_4 is CH_3, R_5 is OCH_3, R_6 is =O, and R_7 is H (Compound **109**).

In another preferred embodiment of the preceding formula, R_1 is H, R_2 is OH, R_3 is H, R_4 is CH_3, R_5 is OCH_3, R_6 is =O, and R_7 is H (Compound **111**).

In yet another preferred embodiment of the preceding formula, R_1 is H, R_2 is OH, R_3 is =O, R_4 is CH_3, R_5 is OCH_3, R_6 is =O, and R_7 is H (Compound **108**).

The subject invention also provides for a method of producing compound 3, comprising reacting a compound having the formula A with a compound having the formula C.

In an embodiment of the preceding method, the reaction is performed in the presence of *N,N*-bis(2-oxo-3-oxazolidinyl)phosphinic chloride.

In another embodiment of the preceding method, the reaction is performed in the presence of Dess-Martin periodinate.

In yet another embodiment of the preceding method, the reaction is further performed in the presence of CH_2Cl_2.

In yet another embodiment of the preceding method, the reaction is performed with H_2, 10%Pd/C, Ethanol-ascetic acid in the presence hydrochloric acid.

This invention also provides a method of producing the compound 3 above, which comprises reacting compound 2 above with H_2, 10%Pd/C, Ethanol-ascetic acid in the presence hydrochloric acid.

This invention also provides a method of producing the compound 2 above, which comprises reacting compound 3 above with camphor sulfonic acid (CSA) in the presence of toluene.

This invention also provides a pharmaceutical composition for treating a tumor in a subject, which comprises a pharmaceutically effective amount of compound 1 above or compound 2 above or compound 3 above.

This invention also provides a method of inhibiting proliferation of tumor cells which comprises contacting the cells under suitable conditions with an effective amount of compound 1 above or compound 2 above or compound 3 above.

This invention also provides a method of treating a patient having a tumor characterized by proliferation of neoplastic cells which comprises administering to the patient an effective amount of compound 1 above or compound 2 above or compound 3 above. In this method the effective amount may be from about 0.5 mg to about 5 mg per day, preferably from about 1 mg to about 3 mg per day, and most preferably about 2 mg per day.

The abbreviation used throughout this disclosure and in the synthesis schemes are abbreviations commonly used in the art of synthetic chemistry and may be readily found in a synthetic chemistry text book.

The abbreviations used in this disclosure are also provided below:

Ac	acetyl
BOC	*t*-butoxycarbonyl
DAM	di(4-methoxyphenyl)methyl
Dmp	dimethylphosphinyl
DMPM	3,4-dimethoxybenzyl
MOM	methoxymethyl
PMB or MPM	*p*-methoxybenzyl or *p*-methoxyphenylmethyl
PMBM	*p*-methoxybenzyloxymethyl
Pv or Piv	pivaloyl
TBS or TBDMS	*t*-butyldimethylsilyl
THF	tetrahydrofuranyl
Tos or Ts	*p*-toluenesulfonyl
BOP-Cl	N,N-bis(2-oxo-3-oxazolidinyl)phosphinic chloride
CSA	camphorsulfonic acid
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DIBAL-H	diisobutylaluminum hydride
DMAP	4-N,N-dimethylaminopyridine
DMF	N,N-dimethylformamide
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone
NBS	N-bromosuccinimide
TFA	trifluoroacetic acid

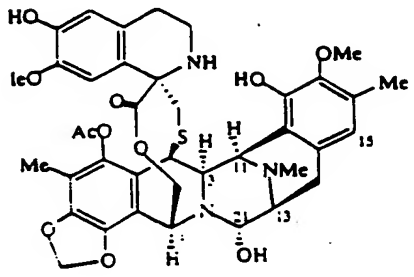
This invention will be better understood from the Experimental Details which follow. However, one skilled in the art will readily appreciate that the specific methods and results discussed are merely illustrative of the invention as described more fully in the claims which follow thereafter.

EXPERIMENTAL DETAILS

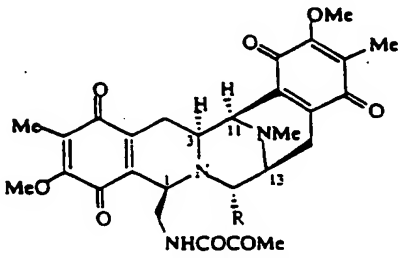
Example 1

Synthetic Explorations in the Saframycin-Ecteinascidin Series: Construction of Major Chiral Subunits Through Catalytic Asymmetric Induction

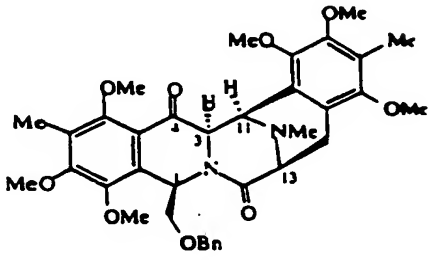
We undertook to test a synthesis directed to systems of the 4-Oxy-saframycin type. From the perspective of its two aromatic sectors, 4-Oxy-saframycin can be viewed as more closely related to compounds of the saframycin series (Saframycin B, A , and S) than to ET.(5) Indeed, the aromatic rings in **III** can be regarded as modified hydroquinone versions of the quinone moieties of saframycin, with the important proviso that **III** also contains a 4-oxo group. This function, in the context of appropriate aromatic domains, is potentially valuable for synthesizing ET and a new range of analogs thereof.



I ET 743

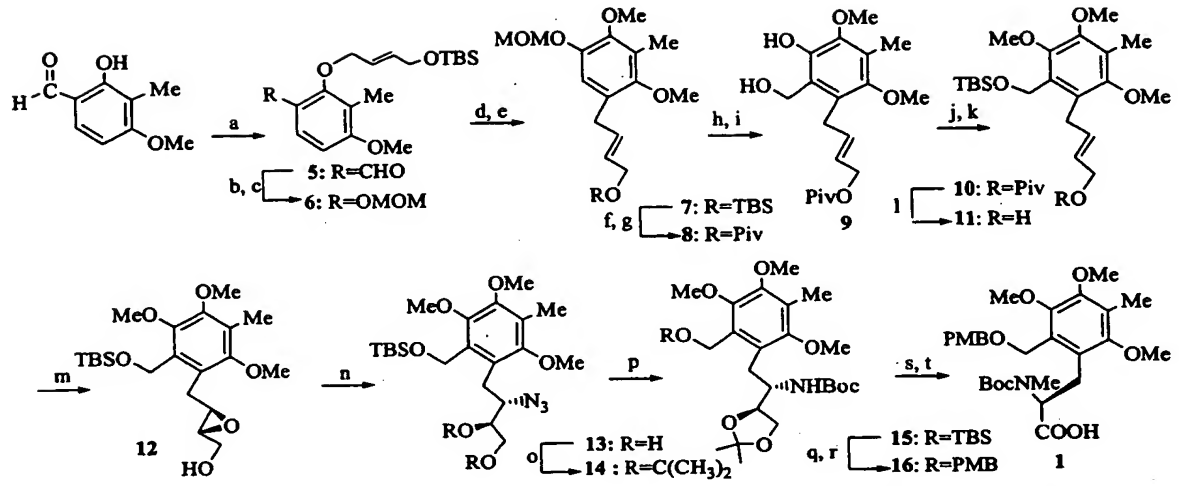


II Saframycin B (R = H)
Saframycin A (R = CN)
Saframycin S (R = OH)



III 4-Oxy-saframycin

Referring to Scheme 1, our approach to **III** contemplated the merger of two moieties, **1** and **2**, wherein each component would bear the absolute configuration appropriate to the goal system in high enantiomeric excess. In this experiment, we describe the pathways, which we followed for reaching the key building blocks. Our inquiry was directed to the applicability of catalytic oxidative asymmetric induction to these targets, and was strongly influenced by precedents from Sharpless.(6 a-c)

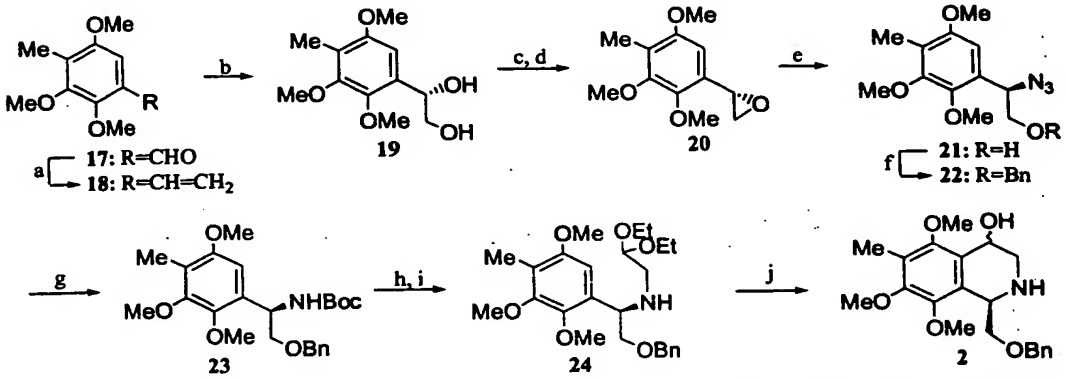


Scheme 1. a) 1.1eq. $BrCH_2CH{=}CHCH_2OTBS$, 1.5eq. K_2CO_3, CH_3CN, reflux, 5h, 100%; b) 1.1eq. 30% H_2O_2, cat. SeO_2, t-BuOH, 40°C, 5h, then Et_3N, MeOH, 85%; c) 1.1eq. MOMCl, 1.5eq. $(i\text{-}Pr)_2NEt$, CH_2Cl_2, 80°C, 12h, 100%; d) 1.1eq. Me_2NPh, toluene, 210°C, 12h, 96%; e) MeI(xs), 1.5eq. K_2CO_3, CH_3CN, reflux, 12h, 87%; f) 1.5eq. TBAF, THF, 1h; g) 1.1eq. PivCl, pyridine-CH_2Cl_2(1:20), 3h; h) 3N HCl, THF-i-PrOH(2:1), 12h, 99% for 3 steps; i) 3eq. Et_2AlCl, $(CH_2O)_n$(xs), CH_2Cl_2, 12h, 96%; j) MeI(xs), 1.5eq. K_2CO_3, $CHCl_3$-MeOH(2:1), reflux, 12 h, 90%; k) 1.2eq. TBSCl, 1.5eq. imidazole, cat. DMAP, CH_2Cl_2, 1h, 99%; l) 2.5eq. DIBAL-H, CH_2Cl_2, -78°C, 30min, 94%; m) 8% (D)-DET, 5.6% $Ti(OiPr)_4$, 2eq. t-BuOOH, m.s. 4Å, -20°C, 1d, 98% (95% ee); n) 3.5eq. $Ti(OiPr)_2(N_3)_2$, PhH, 80°C, 76%(single isomer); o) DMP-acetone(1:2), cat. p-TsOH·H_2O, 10min, 100%; p) H_2, Pd/C, EtOAc, 1.2eq. $(Boc)_2O$, 5h, 100%; q) 1.5eq. TBAF, THF, 1h; r) 1.2 eq. PMBCl, 2eq. NaH, cat. n-BuN^+I^-, THF-DMF(5:1), 5h, 96% for 2 steps; s) MeI(xs), 5eq. NaH, THF-DMF(5:1), 12h, reflux, 93%; t) i, 80% AcOH, 12h; ii, 0.2eq. $KMnO_4$, 4eq. $NaIO_4$, 0.5eq. Na_2CO_3, Dioxane-H_2O(2.5:1), 10h, 95%

We begin with the route followed to reach **1**. The starting material was the readily accessible **4**, (7) obtained from the commercially available 2,4-dimethoxy-3-methyl benzaldehyde. Compound **4** was converted by O-alkylation, as shown to ether **5**. Dakin-like (8) oxidative cleavage of the aryl aldehyde linkage generated a formate, which was de-acylated by trans esterification. Protection of the resultant phenol afforded **6**. The allylic ether had served to protect the C2 hydroxyl group while the substituent at C1 was being adjusted in a constructive way. At this point, p-Claisen rearrangement and sequential protection of the phenol and primary allylic alcohol functions, as indicated, led to **7** and thence **8**. Cleavage of the MOM group was now readily accomplished and the resultant phenol function was exploited to bring about O-hydroxymethylation (see compound

9). Selective methylation of the phenolic hydroxyl and silylation of the primary benzylic alcohol led to compound **10**.

The setting was in place to introduce the L-amino acid functionality. An allylic alcohol (compound **11**) was exposed on cleavage of the pivaloate. Sharpless A.E.,(6a) under the conditions shown, led to **12** in high e.e. (>95%). Azidolysis of the oxirane linkage under titanium mediated direction (6c) afforded a diol **13**. To allow for building the required N-methyl ^{t}Boc linkage, the diol was protected as its acetonide (see structure **14**). From that point, the azide linkage was reductively cleaved in the presence of Boc anhydride to afford **16**. Subsequent to cleavage of the TBS group and installation of a p-methoxybenzyl function, **16** was in hand. Following N-methylation, hydrolysis of the acetonide, and oxidative cleavage of the diol,(9) compound **1** was secured.



Scheme 2. a) 1.6eq. $Ph_3P=CH_2Li$, THF, 0°C, 1h, 96%; b) 1.1eq. AD-mix-α, t-BuOH-H_2O(1:1), 0°C, 3d, 99%; c) 1.1eq. TsCl, pyridine-CH_2Cl_2(1:1), 1d, 95%; d) 2eq. K_2CO_3, MeOH, 4h, 95%; e) 4eq. NaN_3, 15eq. $LiClO_4$, CH_3CN, 60°C, 5h, (2°:1°=6.5:1); f) 1.1eq. BnBr, 5eq. NaH, cat. n-BuN^+I^-, THF, 5h, 90% for 2 steps; g) H_2, Pd/C, EtOAc, 1.2eq. $(Boc)_2O$, 5h, 100%; h) TFA-CH_2Cl_2(1:2), then $NaHCO_3$; i) 4eq. K_2CO_3, 5eq. $BrCH_2CH(OEt)_2$, CH_3CN, reflux, 3d, 80% for 2 steps; j) 12N HCl-THF(1:1), then NaOH, 88% (β-OH:α-OH=4:1).

Referring to scheme 2, the synthesis of **2**, with the suitable S configuration at the future C13, commenced with the known and

readily available benzaldehdye **17**,(10) which was converted to **18**. Asymmetric di-hydroxylation (6b) of the styrene like double bond through the action of AD mix-α gave rise to **19** (> 95% e.e.), from which the epoxide **20** was derived as shown. Azidolysis of the epoxide compound, under the conditions indicated, resulted in a 6.5:1 preference for attack at the benzylic, as opposed to primary carbon. The major product, **21**, was converted to its O-benzyl derivative **22**.

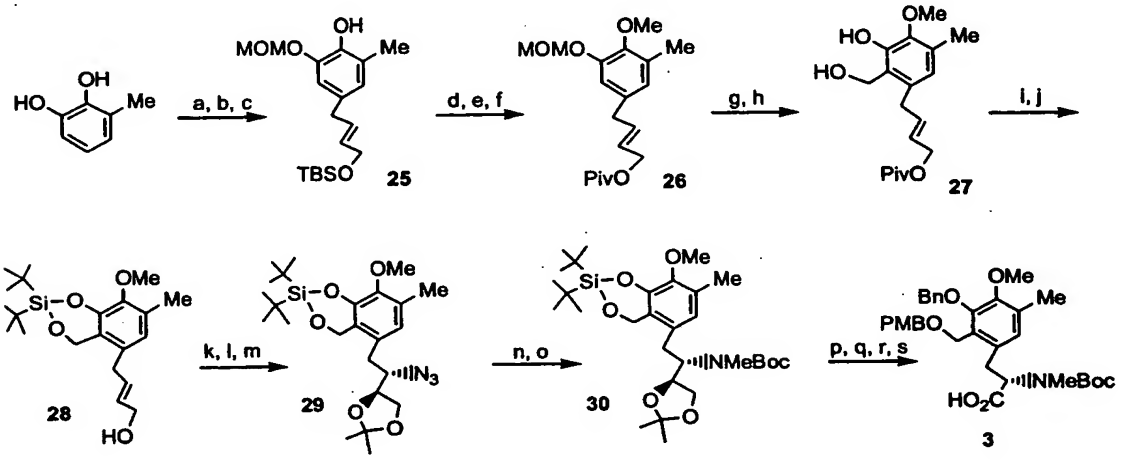
The azide linkage was reduced in the presence of Boc anhydride to afford **23**. The ^{t}Boc protection maneuver was conducted for convenience in the isolation process. Cleavage of the Boc group of **23** was followed by monoalkylation of the resultant amine function with diethylbromoacetal in high yield (see compound **24**). Finally, the tetrahydroisoquinole ring was produced by the Pomerantz-Fritsch type cyclization of **24**.(11) Product **2** was obtained as a 4:1 mixture of β,α stereoisomers at the future C4. As will be seen, this stereochemical issue is without consequence, since this center is destined to become a ketone in short order.

Example 1 shows that a suitably directed p-Claisen rearrangement followed by Sharpless A.E. (6a) can be used to generate a significantly functionalized tyrosine (see compound **1**) analogue. Furthermore, Sharpless A.D., (6b) followed in due course by a modified Pomerantz-Fritsch cyclization, has been used to reach a valuable heavily functionalized tetrahydroisoquinoline subtype **2** in high e.e. Thus, the major subunits needed to reach the targets have been assembled by chemistry, which included p-Claisen rearrangement, asymmetric epoxidation and asymmetric dihydroxylation.

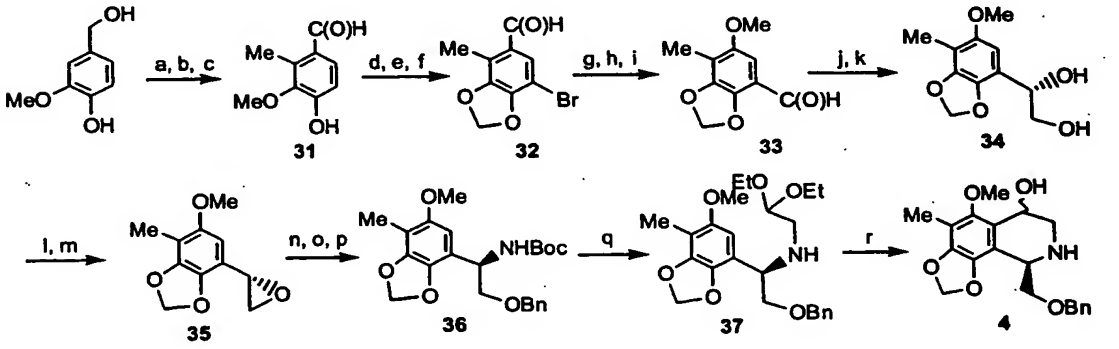
Exampl 2

Construction of Two Additional Chiral Subunits For Use in Preparation of the Saframycin-Ecteinascidin Series

The following Schemes 3 and 4 resulted in two additional subunits, 3 and 4, respectively, which were used to prepare analogues within Saframycin-Ecteinascidin Series.



Scheme 3. a) MOMCl, i-Pr_2NEt, CH_2Cl_2; b) Br⁄⁄OTBS, K_2CO_3, CH_3CN, reflux; c) $PhNMe_2$, Toluene, 210°C, 60% for 3 steps; d) MeI, K_2CO_3,CH_3CN; e) TBAF, THF; f) PivCl, Pyridine, CH_2Cl_2, 91% for 3steps; g) 3N HCl, THF-iPrOH; h) Et_2AlCl, $(CH_2O)_n$, CH_2Cl_2, 84% for 2 steps; i) t-$Bu_2Si(OTf)_2$, 2,6-Lutidine,$CHCl_3$; j) DIBAL-H, CH_2Cl_2, -78°C, 89% for 2 steps; k) SAE, 97%, >95% ee; l) $Ti(OiPr)_2(N_3)_2$, Benzene, reflux; m) DMP, Acetone, p-TsOH, 88% for 3 steps; n) $(Boc)_2O$, H_2, Pd/C, EtOAc; o) MeI, NaH, THF-DMF, reflux, 95% for 2 steps; p) TBAF, THF; q) BnBr, K_2CO_3, $nBu_4N^+I^-$, CHCl3, MeOH; r) PMBCl, NaH, $nBu_4N^+I^-$, THF, DMF, 75% for 3 steps; s) 80% AcOH, then $KMnO_4$, $NaIO_3$, Na_2CO_3, Dioxane-H_2O, 94% for 3 steps



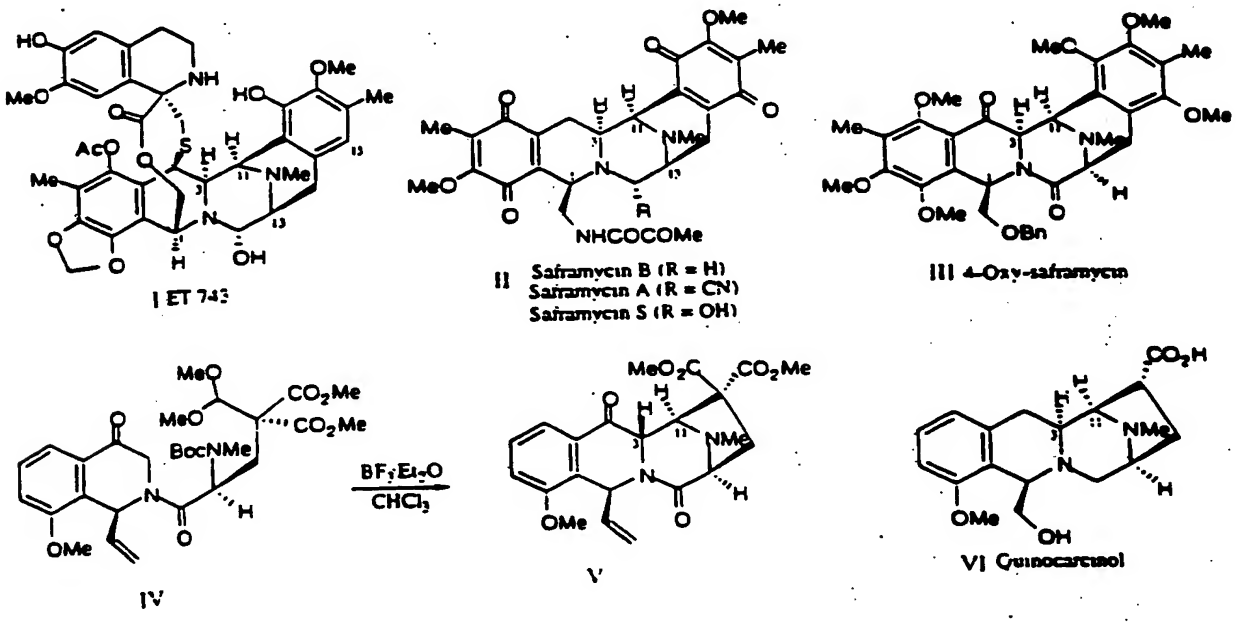
Scheme 4. a) MeOH, TsOH; b) BuLi, MeI, 0 ->10 ->-40°C; c) DDQ, CH_2Cl_2, H_2O, 60 % 3 steps; d) NBS, CH_2Cl_2, 0->10°C, e) BBr_3, CH_2Cl_2; f) $BrCH_2Cl$, CsF, $CsCO_3$, DMF 125°C, 2d; g) i. PhSeSePh, H_2O_2, CH_2Cl_2, 2-3d; ii. K_2CO_3, THF, H_2O; h) Me_2SO_4, NaOH, CH_2Cl_2, H_2O; i) tBuLi, DMF, -78°C; j) $Ph_3P{=}CH_2Li$, THF, 0°C, 1h; 96%; k) AD-mix-α, t-BuOH-H_2O(1:1), 0°C, 1d, 98%; l) TsCl, pyridine-CH_2Cl_2(1:1), 1d, 80%; m) K_2CO_3, MeOH, 7h, 100%; n) NaN_3, $LiClO_4$, CH_3CN, 60°C, 4h, 87%; o) BnBr, 5eq. NaH, cat. n-BuN^+I^-, THF, 5h, 80%; p) H_2, Pd/C, EtOAc, $(Boc)_2O$, 5h, 88%; q) TFA-CH_2Cl_2(1:2), then $NaHCO_3$; then K_2CO_3, $BrCH_2CH(OEt)_2$, CH_3CN, reflux, 3d, >70% for 2 steps; r) 6N Dioxane, H_2O(1:3), then NaOH, 86% (β-OH:α-OH=2:3).

Example 3

A Novel Face Specific Mannich Closure Providing Access to th Saframycin-Ecteinascidin Series of Piperazine Based Alkaloids

Continuing from Example 1, the following uses the building blocks of Example 1 to reach the saframycin-ecteinascidin series.

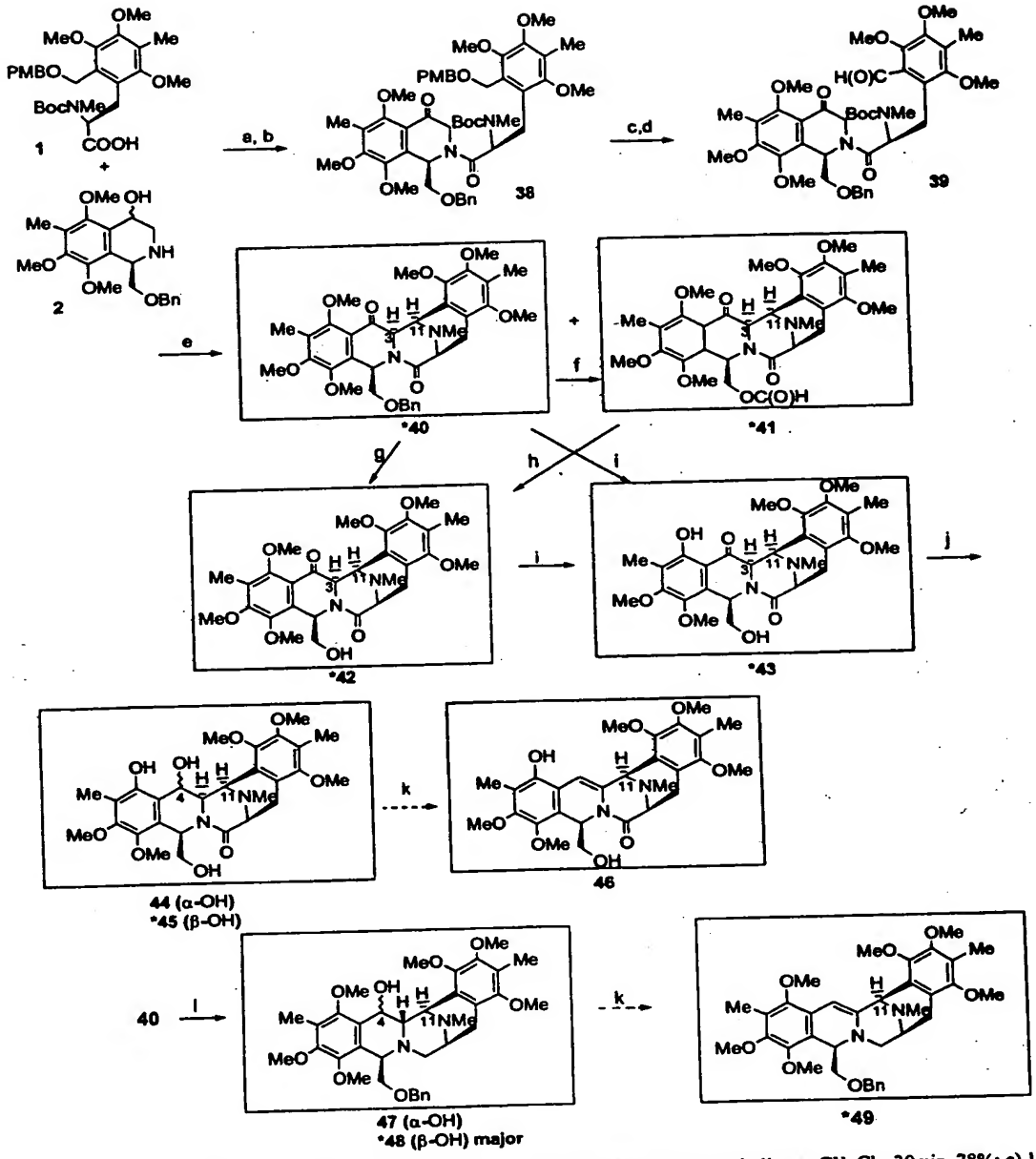
The anti backbone relationship between C3 and C11 in **V**, produced from **IV**, required a sterochemical correction to reach the syn series of quinocarcinol **VI**. Such a C3 - C11 syn relationship also pertains in **I** and **II**. We set as our goal compound **III**. In doing so, we would be revisiting the question of the reasons for the outcome of the backbone stereochemistry in the Mannich closure sequence.



Referring to Scheme 5 below, coupling of **1** and **2** via amide bond formation was accomplished through the action of BOPCl, (12) as shown, in 60 - 65% yield. Oxidation of the diastereomeric alcohol functions gave rise to **38** (75 - 80%), as a homochiral entity. To set the stage for the envisaged annulation, it was necessary to expose the aryl aldehyde

function from its protected benzyl alcohol precursor. Following deprotection and oxidation, the homochiral **39**, bearing the strategic aldehyde, was in hand. However, attempts to reach III by means of a 3-point-attachment of a formic acid equivalent were unsuccessful. Only with aromatic aldehyde in place was the cyclization realized.

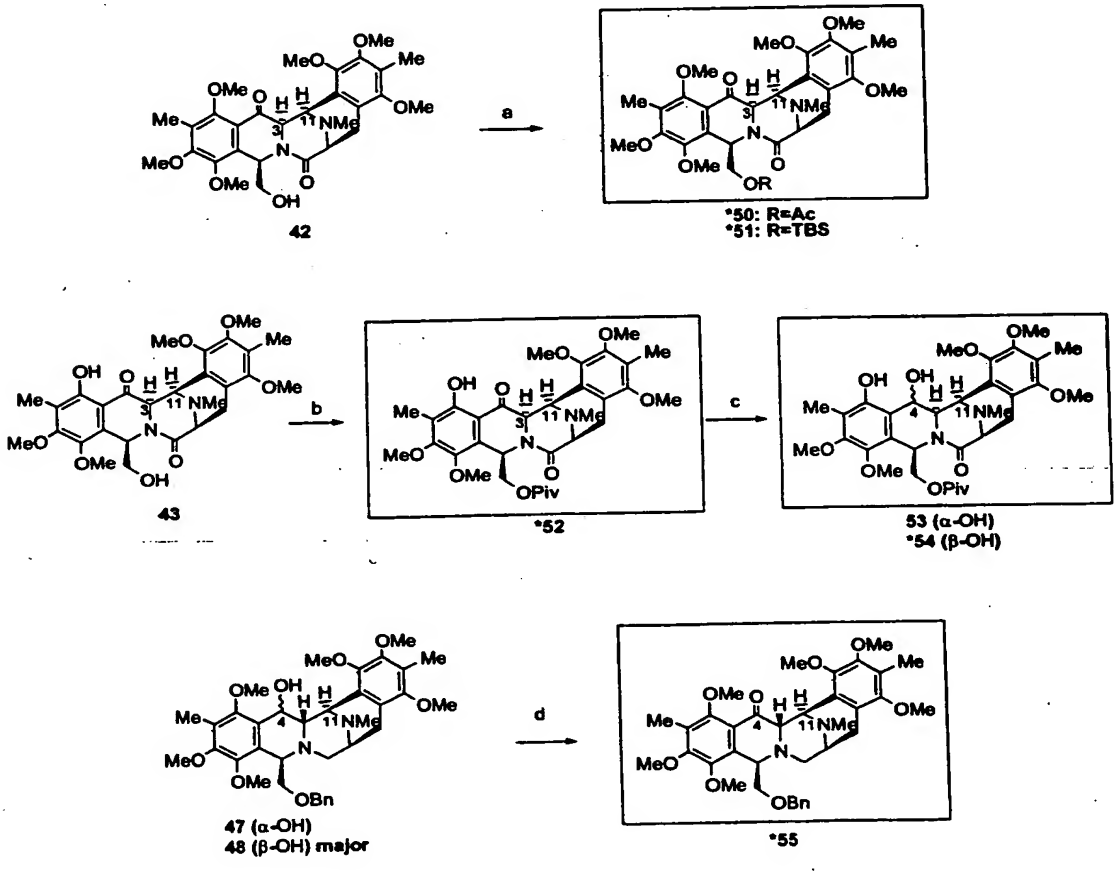
In the event, exposure of compound **39** to the action of formic acid accomplished cleavage of the ^{t}Boc group, thereby triggering Mannich-like double closure to produce **40** (which is also **III**) (75%) and **41** (17%). These products differ only in the "solvolytic" state of the primary center. In a subsequent step, **40** was converted to **41**. Characterization of **40** and **41** by extensive NMR measurements (including COSY, ROESY, HMQC and HMBC techniques) established an unexpected and most welcome result. Not only had cyclization occurred, but also the piperazinone ring had been elaborated with the syn C3-C11 backbone stereochemical relationship required for **I** and **II**. The stereochemistry assigned to **40** (**III**) and **41** was verified by a crystallographic determination at a later stage of the synthetic sequence.



Scheme 5. a) 1.1eq. BOPCl, 2.5eq. Et_3N, CH_2Cl_2, 10h, 63%; b) 1.5eq. Dess-Martin periodinate, CH_2Cl_2, 30min, 78%; c) 1.5eq. DDQ, CH_2Cl_2-buffer7.0-H_2O(20:1:1), 3h, 84%; d) 2eq. NMO, cat. TPAP, m.s. 4Å, CH_2Cl_2, 30min, 84%; e) formic acid, reflux, 10h, 75% for 40, 17% for 41, f) formic acid, reflux; g) H_2, Pd/C, EtOAc, 5h, >50%; h) $NaHCO_3$, MeOH, >50%; i) BBr_3, CH_2Cl_2, 78°C, ~80%; j) $NaBH_4$, MeOH, 0°C, ~50%; k) CSA, Toluene, reflux, 62% for 49; l) AlH_3, THF, 0°C -> r.t., ~70%.

Exampl 4

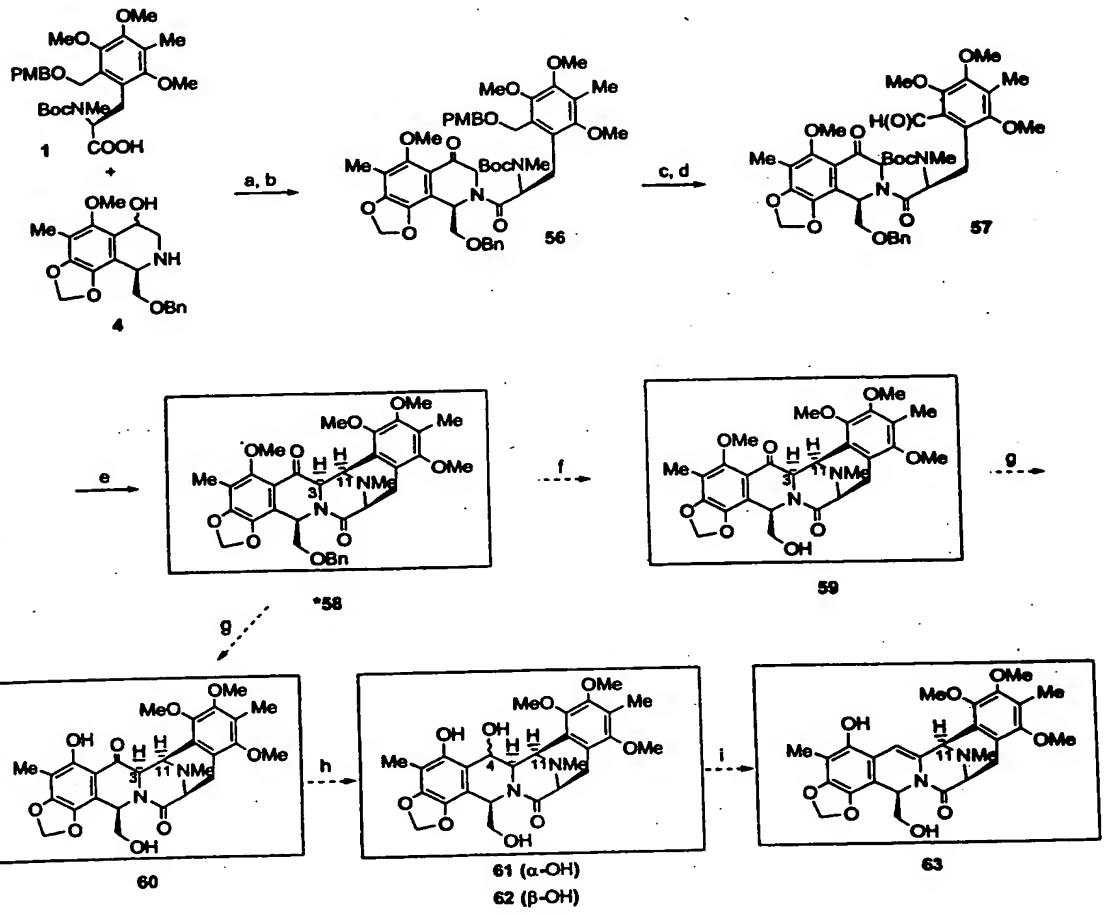
Synthesis of analogue **55** within the Saframycin-Ecteinascidin Series - Scheme 6



Scheme 6. a) AcO_2, Pyridine, CH_2Cl_2, ~70% for **50**; or TBSCl, Imidazole, DMAP (Cat.), ~70% for **51**; b) PivCl Pyridine, CH_2Cl_2, ~60%; c) $NaBH_4$, MeOH, 0°C, ~50%; d) Dess-Martin periodinane Ch_2Cl_2, ~70%.

Example 5

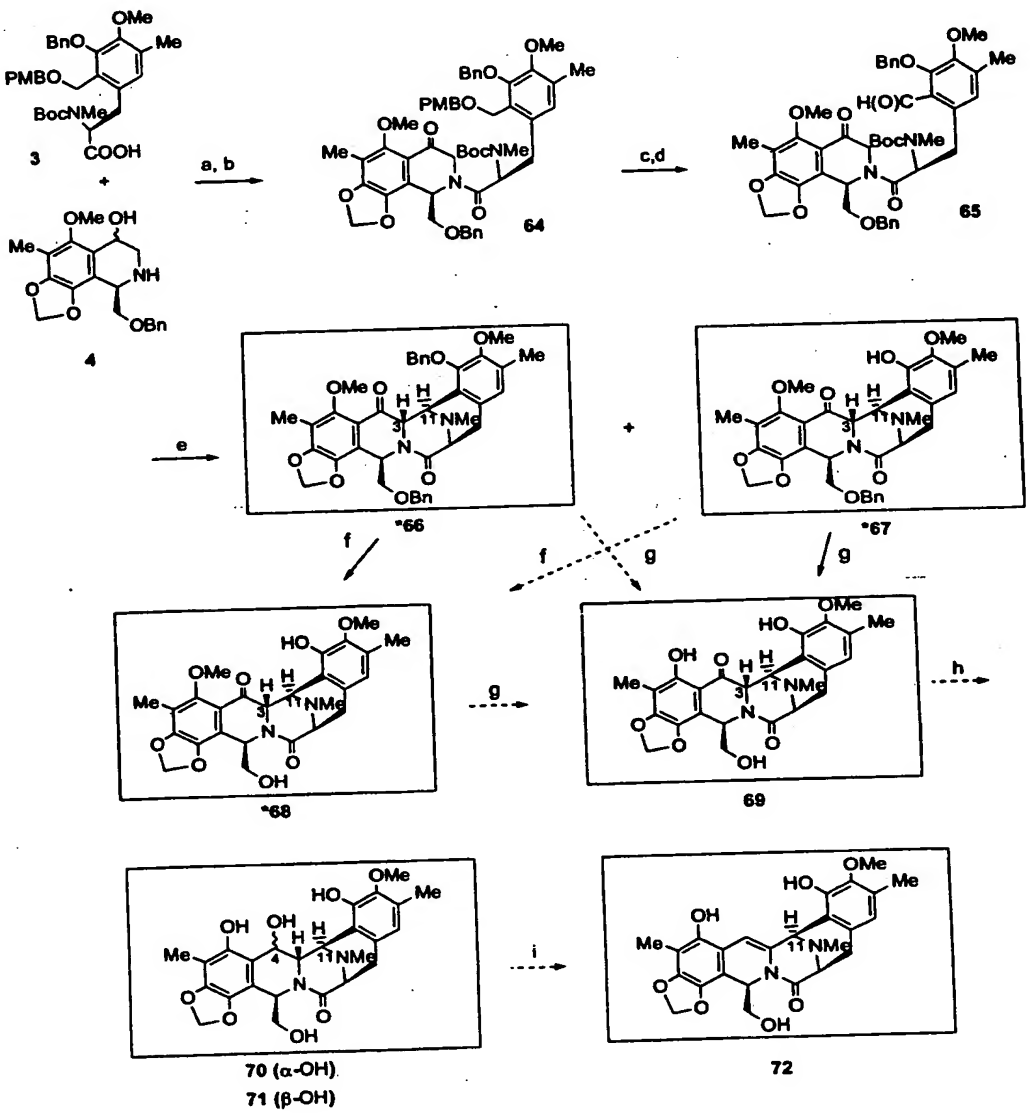
Synthesis of analogue **63** within the Saframycin-Ecteinascidin Series using subunits **1** and **4** - Scheme 7



Scheme 7. a) 1.1eq. BOPCl, 2.5eq. Et_3N, CH_2Cl_2, 10h; b) 1.5eq. Dess-Martin periodinane, CH_2Cl_2, 30 min, ~46% for 2 steps; c) 1.5 eq. DDQ, CH_2Cl_2-buffer7.0-H0(20:1:1), 3h, 80%; d) 2eq. NMO, cat. TPAP, m.s. 4A, CH_2Cl_2, 30 min, 80%; e) formic acid, rflux, 1h, 60-70%; f) H_2, Pd/C, EtOAc, 5h; g) BBr_3, CH_2Cl_2, -78°C; h) $NaBH_4$, MeOH, O°C; i) CSA, Toluene, reflux.

Example 6

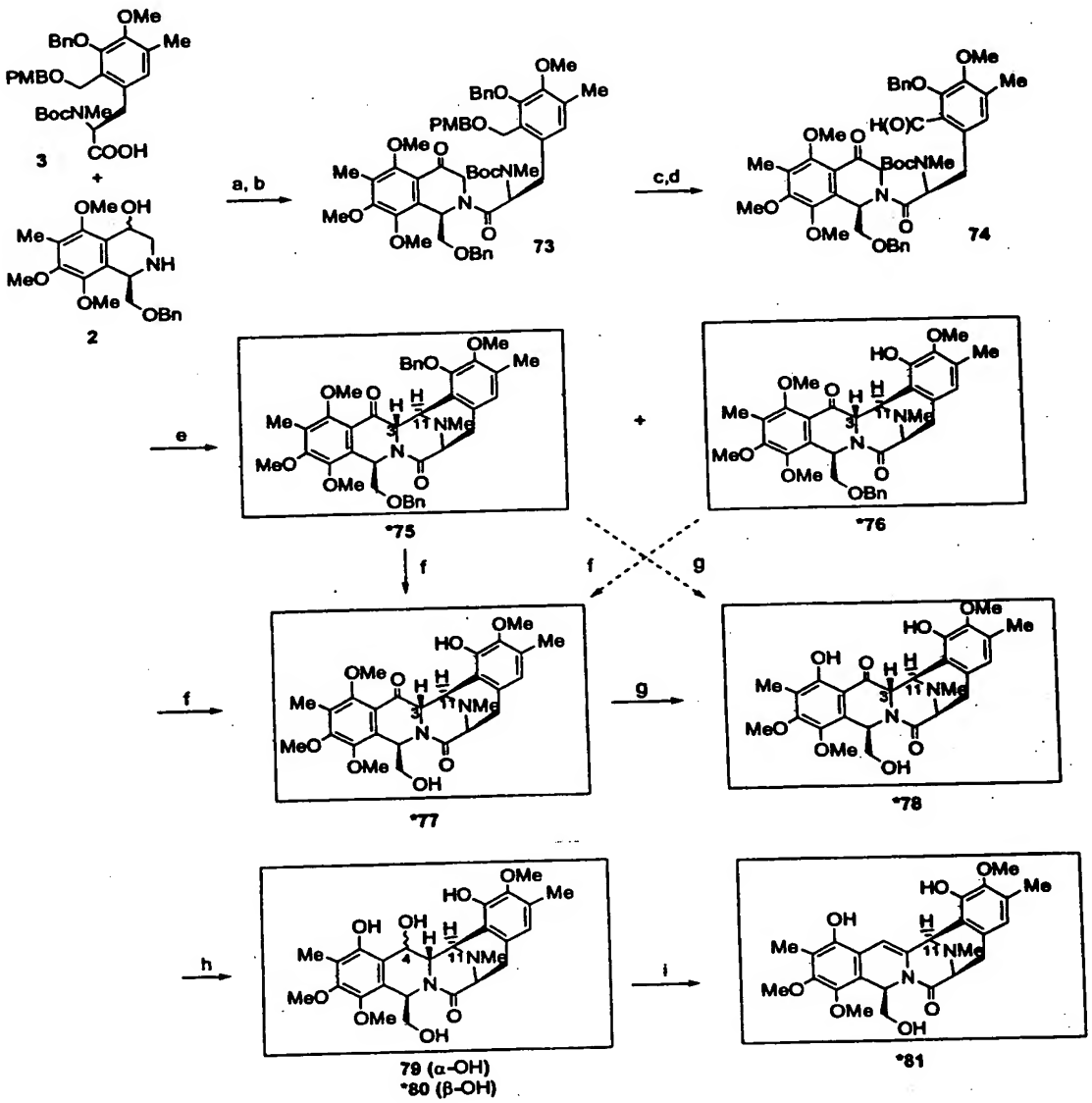
Synthesis of analogues within the Saframycin-Ecteinascidin Series using subunits **3** and **4** - Scheme 8



Scheme 8. a) 1.1eq. BOPCl, 2.5 eq. Et_3N, CH_2Cl_2, 10h; b) 1.5eq. Dess-Martin periodinane, Ch_2Cl_2, 30min. ~48% for 2 steps; c) 1.5eq. DDQ, CH_2Cl_2-buffer7.0-H_2O(20:1:1), 3h, 80%; d) 2 eq. NMO, cat. TPAP, m.s 4A, CH_2Cl_2, 30min, 80%; e) formic acid, reflux, 1h, 60-70%, (66:67=~5:1); f) H_2, Pd/C, EtOAc, 5H, >90%; g) BBr_3, Ch_2Cl_2, -78°C; h) $NaBH_4$ MeOH, 0°C; i) CSA, Toluene, reflux.

Example 7

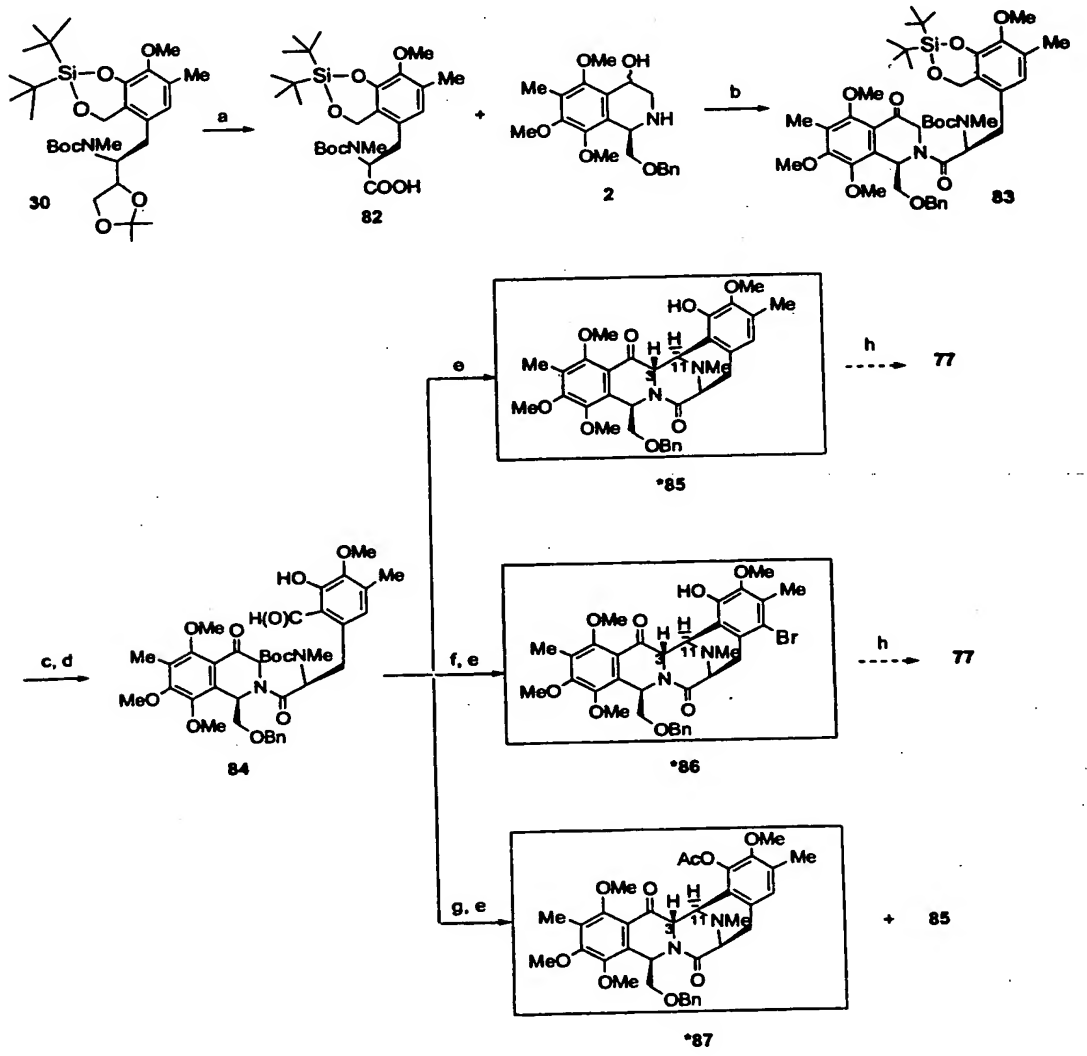
Synthesis of analogues within the Saframycin-Ecteinascidin Series using subunits **3** and **2** - Scheme 9



Scheme 9. a) 1.1.eq. BOPCl, 2.5eq. ET_3N, CH_2CL_2, 10h; b) 1.5eq.Dess-Martin periodinane, CH_2Cl_2, 30min, ~50% for 2 steps; c) 1.5eq. DDQ, CH_2CL_2-buffer 7.0-H_2O (20:1:1), 3h, 70-80%; d) 2eq. NMO, cat. TPAP, m.s. 4A, CH_2Cl_2, 30min, 70-80%; e) formic acid, reflux, 1h, 60-70% (75:76=5:1); f) H_2, Pd/C, EtOAc, 5h; g) BBr_3, CH_2Cl_2, -78°C 93-99%; h) $NaBH_4$, MeOH, 0°C, 50%; i) CSA, Toluene, reflux, 92%.

Example 8

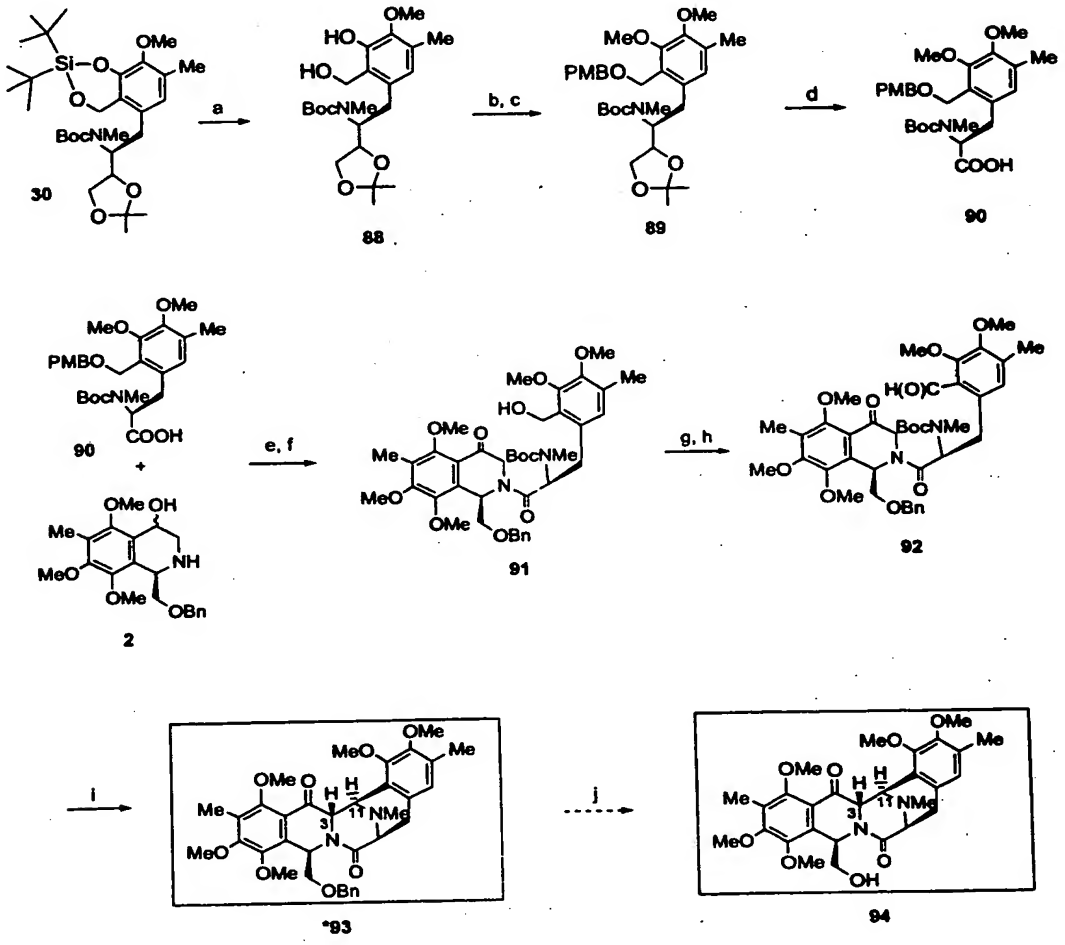
Synthesis of analogues within the Saframycin-Ecteinascidin Series - Scheme 10



Scheme 10. a) 80% AcOH, 10h, then $KMnO_4$, $NaIO_4$, Na_2CO_3; Dioxane, H_2O, >90%; b) i.1.1eq. BOPCl, 2.5eq. ET_3N, CH_2Cl_2, 10h; ii. Dess-Martin periodinane, CH2Cl2, 60% for 2 steps; c) HF-Py, THF, AcOH (Cat), 93%; d) MnO_2, acetone, 72%; e) formic acid, reflux, 1h, 60-70%; f) Br_2 or NBS, CCl_4, ~60%; g) Ac_2O, Pyridine, Ch_2Cl_2, ~70%, (87:85=1:1); h) H_2, Pd/C, Et)Ac.

Exampl 9

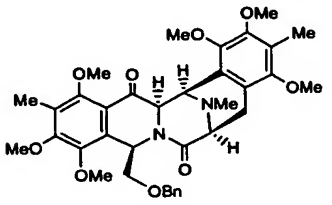
Synthesis of analogues within the Saframycin-Ecteinascidin Series - Scheme 11



Scheme 11. a) TBAF, THF,>90%; b) MeI, K_2C0_3, $CHCl_3$,MeOH, reflux, 80%; c) PMBCl, MaH, nBuN$^+$T, THF, DMF, 90%; d) 80%AcOH, 10h, then $KMn0_4$, $NaI0_4$, Na_2CO_3, Dioxane, H_20, 90% for steps; e) 1.1eq. BOPCl, 2.5eq. Et_3N, CH_2Cl_2, 10h; f) Des-Martin periodinane, CH_2Cl_2, ~50% for 2 steps; g) DDQ, CH_2Cl_2, H_20, Buffer 7.0, 85%; h) NMO, TPAP, 4A ms, CH_2Cl_2, 70%, i)formic acid, reflux, 1h, 60-70%; j) H_2, Pd/C, Et)Ac.

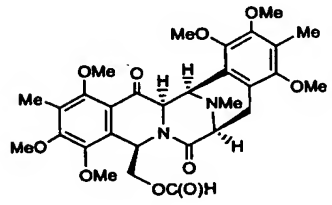
Mass Spectroscopy and ^{1}H-NMR Data for Selected Compounds

The following table provides the ^{1}H-NMR and MS data for selected compounds which are useful as cytotoxic agents:



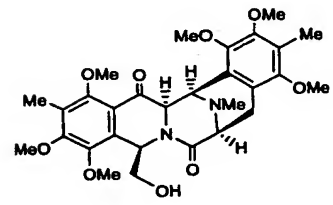
40

^{1}H NMR ($CDCl_3$, 500 MHz) 7.24-7.10 (m, 5H), 6.14 (t, J = 3.4 Hz, 1H), 5.08 (d, J = 3.6 Hz, 1H), 4.66 (d, J = 3.1 Hz, 1H), 4.52 (d, J = 12.2 Hz, 1H), 4.32 (d, J = 12.2 Hz, 1H), 4.0-3.5 (m, 3H), 3.88 (m, 1H), 3.80 (s, 3H), 3.77 (s, 3H), 3.76 (s, 3H), 3,67 (s, 3H), 3.55 (s, 3H), 3.54 (s, 3H), 3.01 (m, 2H), 2.51 (s, 3H), 2.03 (s, 6H); HRMS (FAB +) *m/z* calcd for $C_{36}H_{42}O_9N_2K$ 658.2527, found 658.2557.



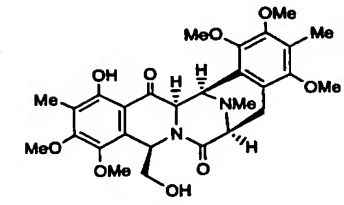
41

^{1}H NMR ($CDCl_3$, 500 MHz) 7.93 (s, 1H), 6.24 (dd, J = 6.2 Hz, 3.3 Hz, 1H), 5.02 (d, J = 3.6 Hz, 1H), 4.65 (d, J = 2.8 Hz, 1H), 4.38 (dd, J = 11.5 Hz, 6.4 Hz, 1H), 4.29 (d, J = 11.6 Hz, 2.6 Hz, 1H), 3.79 (s, 3H), 3.78 (s, 3H), 3.76 (s, 3H), 3.72 (m, 1H), 3.66 (s, 3H), 3.62 (s, 3H), 3.02-2.90 (m, 2H), 2.52 (s, 3H), 2.02 (s, 3H), 2.01 (s, 3H); HRMS (FAB +) *m/z* calcd for $C_{30}H_{36}O_{10}N_2K$ 623.2007, found 623.2008.



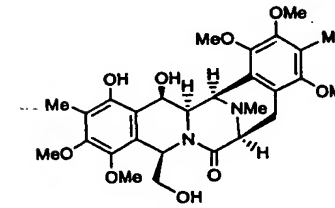
42

^{1}H NMR ($CDCl_3$, 500 MHz) 6.08 (dd, J = 7.7 Hz, 4.4 Hz, 1H), 5.03 (d, J = 3.5 Hz, 1H), 4.69 (d, J = 2.0 Hz, 1H), 4.0-3.5 (m, 3H), 3.80 (s, 3H), 3.79 (s, 3H), 3.77 (s, 3H), 3.56 (m, 1H), 3.54 (s, 3H), 2.95 (m, 2H), 2.56 (s, 3H), 2.07 (s, 6H). MS(ESI+) 577.0.



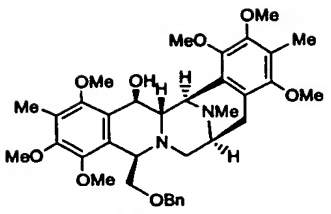
43

^{1}H NMR ($CDCl_3$, 500 MHz) 10.99 (s, 1H), 5.94 (t, J = 3.9 Hz, 1H), 5.12 (d, J = 3.0 Hz, 1H), 4.67 (s, 1H), 3.88 (m, 1H), 3.8-3.5 (m, 2H), 3.78 (s, 3H), 3.71 (s, 3H), 3.68 (s, 3H), 3.55 (s, 3H), 3.45 (s, 3H), 3.00 (m, 2H), 2.58 (s, 3H), 2.02 (s, 3H), 1.98 (s, 3H); MS(ESI +) *m/z* 543.6.



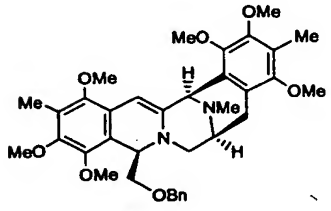
45

^{1}H NMR ($CDCl_3$, 500 MHz) 5.88 (dd, J = 7.4 Hz, 3.7 Hz, 1H), 5.19 (d, J = 6.1 Hz, 2.8 Hz, 1H), 4.63 (dd, J = 5.9 Hz, 2.9 Hz, 1H), 4.52 (d, J = 5.1 Hz, 1H), 4.05 (m, 1H), 3.95 (s, 3H), 3.83 (m, 1H), 3.744 (s, 6H), 3.737 (s, 3H), 3.71 (m, 1H), 3.62 (s, 3H), 3.48 (m, 2H), 3.13 (dd, J = 18.4 Hz, 8.4Hz, 1H), 2.85 (d, J = 18.4 Hz, 1H), 2.52 (s, 3H), 2.14 (s, 3H), 2.07 (s, 3H); MS(ESI +) *m/z* 545.6.



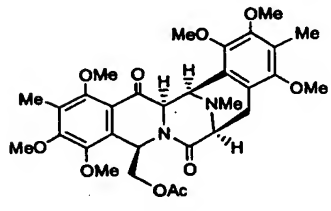
48

^{1}H NMR ($CDCl_3$, 500 MHz) 7.30-7.15 (m, 5H) , 5.08 (s, 1H), 4.45 (s, 2H), 4.26 (m, 2H), 3.90-3.70 (m,2H), 3.85 (s, 3H), 3.71 (s, 3H), 3.63 (s, 6H), 3.61 (s, 3H), 3.583 (s, 3H), 3.577 (s, 3H), 3.56 (m, 1H), 3.54 (d, J = 10.2 Hz, 1H), 3.35 (br s, 1H), 3.24 (d, J = 12.4 Hz, 1H), 3.15 (br s, 1H), 3.00 (dd, J = 18.3 Hz, 8.3 Hz, 1H), 2.78 (d, J = 18.4 Hz, 1H), 2.20 (s, 3H), 2.15 (s, 6H); MS(ESI +) *m/z* 635.3.



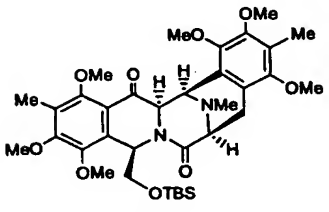
49

^{1}H NMR ($CDCl_3$, 500 MHz) 7.28-7.16 (m, 5H), 5.09 (dd, J = 8.7 Hz, 4.1 Hz, 1H), 5.45 (s, 2H), 4.28 (d, J = 5.2 Hz, 2H), 4.18 (s, 1H), 3.82 (s, 3H), 3.68 (s, 3H), 3.63 (s, 3H), 3.60 (s, 3H), 3.58 (s, 3H), 3.57 (s, 3H), 3.84-3,38 (m, 5H), 3.24 (m, 1H), 3.06 (m, 2H), 2.66 (d, J = 17.6 Hz, 1H), 2.18 (s, 3H), 2.02 (s, 6H); MS (APCI +) *m/z* 604.0.



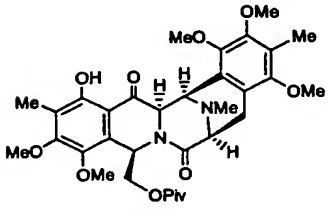
50

^{1}H NMR ($CDCl_3$, 500 MHz) 6.18 (t, J = 2.9 Hz, 1H), 5.04 (d, J = 3.5 Hz, 1H), 4.63 (d, J = 3.0 Hz, 1H), 4.38 (dd, J = 11.6 Hz, 4.6 Hz, 1H), 4.2 (dd, J = 11.6 Hz, 2.6 Hz, 1H), 3.67 (s, 3H), 3.79 (s, 3H), 3.78 (s, 3H), 3.76 (s, 3H), 3.71 (d, J = 6.5 Hz, 1H), 3.57 (s, 3H), 3.55 (s, 3H), 2.98 (m, 2H), 2.53 (s, 3H), 2.02 (s, 3H), 2.01 (s, 3H), 1.92 (s, 3H); MS(ESI +) *m/z* 599.5.



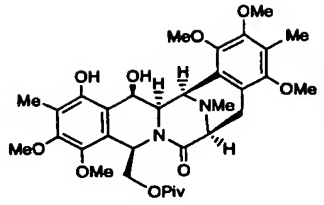
51

^{1}H NMR ($CDCl_3$, 400 MHz) 5.92 (s, 1H), 5.10 (s, 1H), 4.63 (s, 1H), 4.08 (m, 1H), 3.89 (m, 1H), 3.81 (s, 3H), 3.76 (s, 3H), 3.75 (s, 3H), 3.66 (m, 1H), 3.51 (s, 3H), 3.44 (s, 3H), 2.97 (m, 2H), 2.54 (s, 3H), 2.02 (s, 6H); MS(ESI +) *m/z* 670.8.



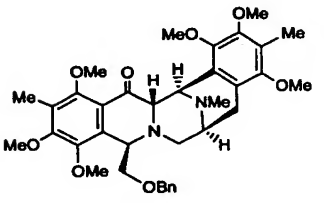
52

^{1}H NMR ($CDCl_3$, 400 MHz) 11.01 (s, 1H), 6.09 (s, 1H), 5.07 (d, J = 3.0 Hz, 1H), 4.68 (s, 1H), 4.30 (m, 1H), 4.15 (m, 1H), 4.0-3.5 (m, 1H), 3.76 (s, 3H), 3.71 (s, 6H), 3.52 (s, 3H), 3.44 (m, 1H), 3.51 (s, 3H), 3.44 (s, 3H), 2.99 (m, 2H), 2.56 (s, 3H), 2.03 (s, 6H), 1.07 (s, 9H); MS(ESI +) *m/z* 628.0.



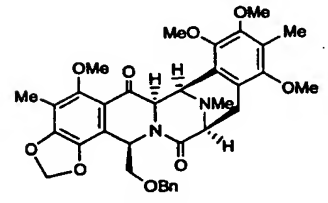
54

^{1}H NMR ($CDCl_3$, 500 MHz) 6.08 (dd, J = 7.7 Hz, 2.8 Hz, 1H), 5.77 (s, 1H), 5.17 (s, 1H), 4.52 (m, 1H), 4.37 (m, 1H), 3.95 (s, 3H), 3.77 (s, 6H), 3.73 (s, 3H), 3.66 (s, 3H), 3.12 (m, 1H), 2.89 (d, J = 18.4 Hz, 1H), 2.45 (s, 3H), 2.14 (s, 3H), 2.07 (s, 3H), 1.14 (s, 9H); MS(ESI +) *m/z* 630.0.



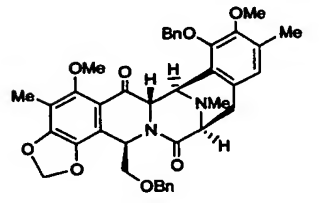
55

^{1}H NMR ($CDCl_3$, 500 MHz) 7.24-7.12 (m, 5H), 4.66 (s, 1H), 438 (d, J = 12.1 Hz, 1H), 4.28 (d, J = 12.1 Hz, 1H), 4.16 (d, J= 2.7 Hz, 1H), 4.04 (s, 1H), 3.82-3.71 (m, 1H), 3.78 (s, 3H), 3.76 (s, 3H), 3.75(s, 3H), 3,65 (s, 3H), 3.55 (s, 3H), 3.54 (s, 3H), 3.53 (dd, J= 10.1Hz, 5.2 Hz, 1H), 3.47 (m, 1H), 2.90 (m, 2H), 2.49 (d, J= 8.0 Hz, 1 H), 2.28 (s, 3H), 2.15 (s, 3H), 2.14 (s, 3H); MS (ESI +) *m/z* 634.4.



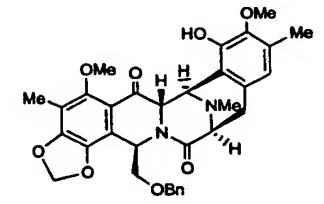
58

^{1}H NMR ($CDCl_3$, 500 MHz) 7.23 (m, 3H), 7.10 (d, J = 7.1 Hz, 2H), 5.88 (d, J = 6.3 Hz, 2H), 5.85 (t, J = 3.8 Hz, 1H), 5.06 (d, J = 3.2 Hz, 1H), 4.63 (d, J = 2.6 Hz, 1H), 4.48 (d, J = 12.2 Hz, 1H), 4.34 (d, J = 12.2 Hz, 1H), 3.83 (m, 3H), 3.82 (m, 1H), 3.75 (s, 3H), 3.66 (d, J = 5.8 Hz, 1H), 3.57 (s, 4H), 3.50 (s, 3H), 2.98 (m, 2H), 2.50 (s, 3H), 2.03 (s, 3H), 1.99 (s, 3H); MS (APCI) *m/z* 631.0.



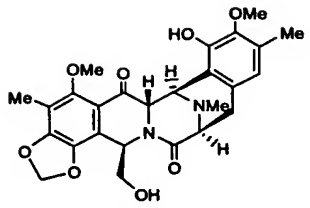
66

^{1}H NMR ($CDCl_3$, 500 MHz) 7.50 (d, J = 7.5 Hz, 2H), 7.32 (m, 3H), 7.10 (m, 3H), 6.79 (d, J = 7.4 Hz, 2H), 6.64 (s, 1H), 6.06 (m, 1H), 5.94 (s, 2H), 5.17 (s, 1H), 5.12 (d, J = 10.9 Hz, 1H), 5.01 (d, J = 10.8 Hz, 1H), 4.52 (s, 1H), 4.11 (m, 1H), 4.01 (d, J = 9.4 Hz, 1H), 3.83 (s, 3H), 3.66 (m, 2H), 3.60 (s, 3H), 3.59 (m, 1H), 3.13 (m, 1H), 2.78 (d, J = 17.3 Hz, 1H), 2.25 (s, 3H), 2.18 (s, 3H), 2.14 (s, 3H); MS (FAB +) *m/z* 667.4.



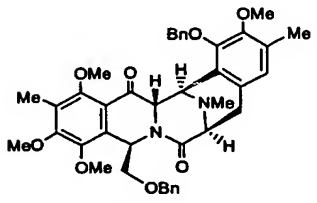
67

^{1}H NMR ($CDCl_3$, 500 MHz) 7.16 (m, 3H), 6.82 (m, 2H), 6.45 (s, 1H), 6.10 (dd, J = 6.4 Hz, 3.5 Hz, 1H), 5.97 (d, J = 2.0 Hz, 2H), 5.67 (s, 1H), 5.24 (s, 1H), 4.56 (s, 1H), 4.10 (m, 2H), 3.85 (s, 3H), 3.70-3.60 (m, 2H), 3.68 (s, 3H), 3.14 (dd, J = 17.3 Hz, 7.8 Hz, 1H), 2.80 (d, J = 17.3 Hz, 1H), 2.40 (s, 3H), 2.20 (s, 3H), 2.14 (s, 3H); MS (ESI +) *m/z* 587.1.



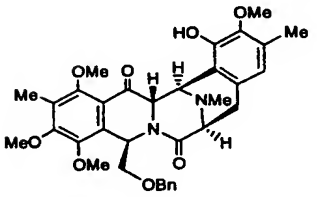
68

^{1}H NMR ($CDCl_3$, 500 MHz) 6.47 (s, 1H), 6.04 (s, 1H), 6.00 (s, 1H), 5.99 (m, 1H), 5.24 (s, 1H), 4.28 (s, 1H), 3.90-3.70 (m, 2H), 3.80 (s, 3H), 3.74 (s, 3H), 3.65 (d, J = 6.5 Hz, 1H), 3.13 (dd, J = 16.2 Hz, 9.0 Hz, 1H), 2.78 (d, J = 16.2 Hz, 1H), 2.42 (s, 3H), 2.22 (s, 3H), 2.13 (s, 3H); MS (FAB +) *m/z* 497.1.



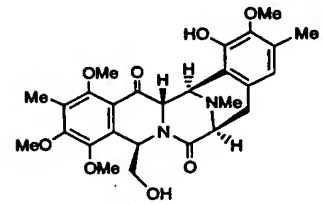
75

^{1}H NMR ($CDCl_3$, 500 MHz) 7.54 (d, J = 7.3 Hz, 2H), 7.35-7.25 (m, 3H), 7.10 (m, 3H), 6.81 (d, J = 7.2 Hz, 2H), 6.65 (s, 1H), 6.26 (dd, J = 7.8 Hz, 3.5 Hz, 1H), 5.13 (s, 1H), 5.12 (d, J = 10.8 Hz, 1H), 5.04 (d, J = 10.8 Hz, 1H), 4.46 (s, 1H), 4.14 (d, J = 11.8 Hz, 1H), 3.99 (d, J = 11.8 Hz, 1H), 3.84 (s, 3H), 3.82 (s, 3H), 3.80 (s, 3H), 3.70 (dd, J = 10.9 Hz, 3.6 Hz, 1H), 3.61 (s, 3H), 3.59 (m, 1H), 3.11 (dd, J = 17.3 Hz, 6.8 Hz, 1H), 2.76 (d, J = 17.3 Hz, 1H), 2.22 (s, 3H), 2.172 (s, 3H), 2.169 (s, 3H); HRMS (FAB +) *m/z* calcd for $C_{41}H_{45}O_8N_2$ 693.3176, found 693.3168.



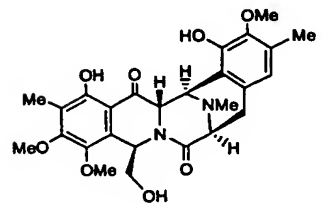
76

^{1}H NMR ($CDCl_3$, 500 MHz) 7.16 (m, 3H), 6.84 (m, 2H), 6.45 (s, 1H), 6.30 (dd, J = 7.5 Hz, 3.8 Hz, 1H), 5.72 (s, 1H), 5.21 (s, 1H), 4.48 (s, 1H), 4.18 (d, J = 11.8 Hz, 1H), 4.07 (d, J = 11.8 Hz, 1H), 3.90-3.70 (m, 2H), 3.85 (s, 3H), 3.83 (s, 3H), 3.80 (s, 3H), 3.73 (s, 3H), 3.70-3.65 (m, 1H), 3.15 (dd, J = 17.3 Hz, 6.8 Hz, 1H), 2.79 (d, J = 17.3 Hz, 1H), 2.38 (s, 3H), 2.19 (s, 3H), 2.17 (s, 3H); MS (ESI +) *m/z* 603.3.



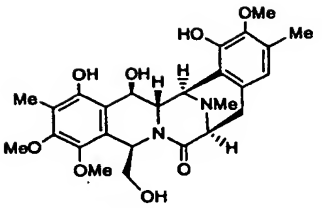
77

^{1}H NMR ($CDCl_3$, 500 MHz) 6.51 (s, 1H), 6.15 (dd, J = 8.5 Hz, 4.4 Hz, 1H), 5.77 (s, 1H), 5.20 (s, 1H), 4.23 (s, 1H), 3.90 (s, 3H), 3.90-3.70 (m, 2H), 3.89 (s, 3H), 3.81 (s, 3H), 3.76 (s, 3H), 3.65 (m, 1H), 3.15 (dd, J = 17.3 Hz, 6.7 Hz, 1H), 2.77 (d, J = 17.3 Hz, 1H), 2.40 (s, 3H), 2.24 (s, 3H), 2.18 (s, 3H); MS (ESI +) *m/z* 513.5.



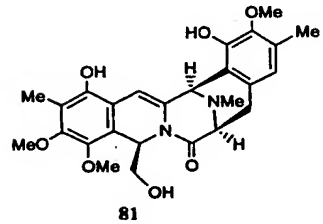
78

^{1}H NMR ($CDCl_3$, 500 MHz) 12.26 (s, 1H), 6.50 (s, 1H), 6.15 (dd, J = 7.2 Hz, 4.3 Hz, 1H), 5.86 (s, 1H), 5.21 (s, 1H), 4.41 (s, 1H), 3.88 (s, 3H), 3.82 (s, 3H), 3.80 (m, 1H), 3.76 (s, 3H), 3.67 (m, 2H), 3.15 (dd, J = 17.4 Hz, 6.7 Hz, 1H), 2.78 (d, J = 17.4 Hz, 1H), 2.38 (s, 3H), 2.24 (s, 3H), 2.11 (s, 3H); MS (ESI +) *m/z* 500.1.



80

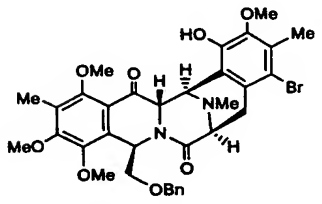
^{1}H NMR ($CDCl_3$, 500 MHz) 6.50 (s, 1H), 5.76 (dd, J = 8.2 Hz, 4.1 Hz, 1H), 5.24 (m, 1H), 4.50 (s, 1H), 3.90-3.60 (m, 13H), 3.46 (m, 1H), 3.12 (dd, J = 17.4 Hz, 6.1 Hz, 1H), 2.68 (d, J = 17.4 Hz, 1H), 2.42 (s, 3H), 2.18 (s, 3H), 2.12 (s, 3H); MS (ESI +) *m/z* 501.4.



81

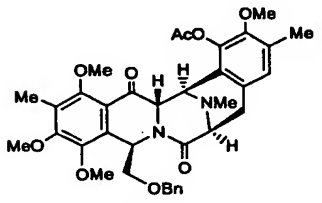
^{1}H NMR ($CDCl_3$, 500 MHz) 6.52 (s, 1H), 6.26 (s, 1H), 6.04 (s, 1H), 5.81 (br s, 1H), 4.62 (s, 1H), 3.83 (s, 3H), 3.82 (m, 1H), 3.79 (s, 3H), 3.70 (s, 3H), 3.55 (m, 2H), 3.29 (m, 2H), 3.15 (br s, 1H), 3.14 (d, J = 17.4 Hz, 1H), 2.54 (s, 3H), 2.22 (s, 3H), 2.02 (s, 3H); MS (ESI +) *m/z* 483.5.

^{1}H NMR (CD_3OD, 500 MHz) 6.50 (s, 1H), 6.48 (s, 1H), 5.95 (t, J = 6.7 Hz, 1H), 4.67 (s, 1H), 3.81 (s, 3H), 3.75 (s, 3H), 3.67 (s, 3H), 3.62 (d, J = 6.2 Hz, 1H), 3.34 (S, 1H), 3.08 (dd, J = 10.8 Hz, 6.3 Hz, 1H), 2.95 (m, 2H), 2.51 (s, 3H), 2.21 (s, 3H), 2.11 (s, 3H).



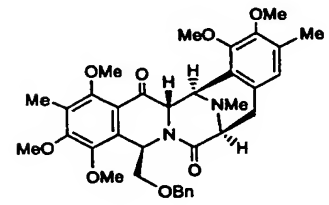
86

^{1}H NMR ($CDCl_3$, 500 MHz) 7.40-7.15 (m, 5H), 6.84 (s, 1H), 6.29 (m, 1H), 5.72 (s, 1H), 5.22 (s, 1H), 4.51 (s, 1H), 4.22 (d, J = 11.5 Hz, 1H), 4.09 (d, J = 11.5 Hz, 1H), 3.90-3.60 (m, 15H), 2.95 (m, 2H), 2.38 (s, 3H), 2.36 (s, 3H), 2.14 (s, 3H); MS (ESI +) *m/z* 682.9.



87

^{1}H NMR ($CDCl_3$, 500 MHz) 7.20-6.80 (m, 5H), 6.79 (s, 1H), 6.28 (m, 1H), 5.28 (s, 1H), 4.34 (s, 1H), 4.20 (m, 1H), 4.08 (m, 1H), 4.85-3.60 (m, 15H), 3.47 (m, 1H), 3.15 (m, 1H), 2.84 (d, J = 17.3 Hz, 1H), 2.35 (s, 3H), 2.33 (s, 3H), 2.28 (s, 3H).



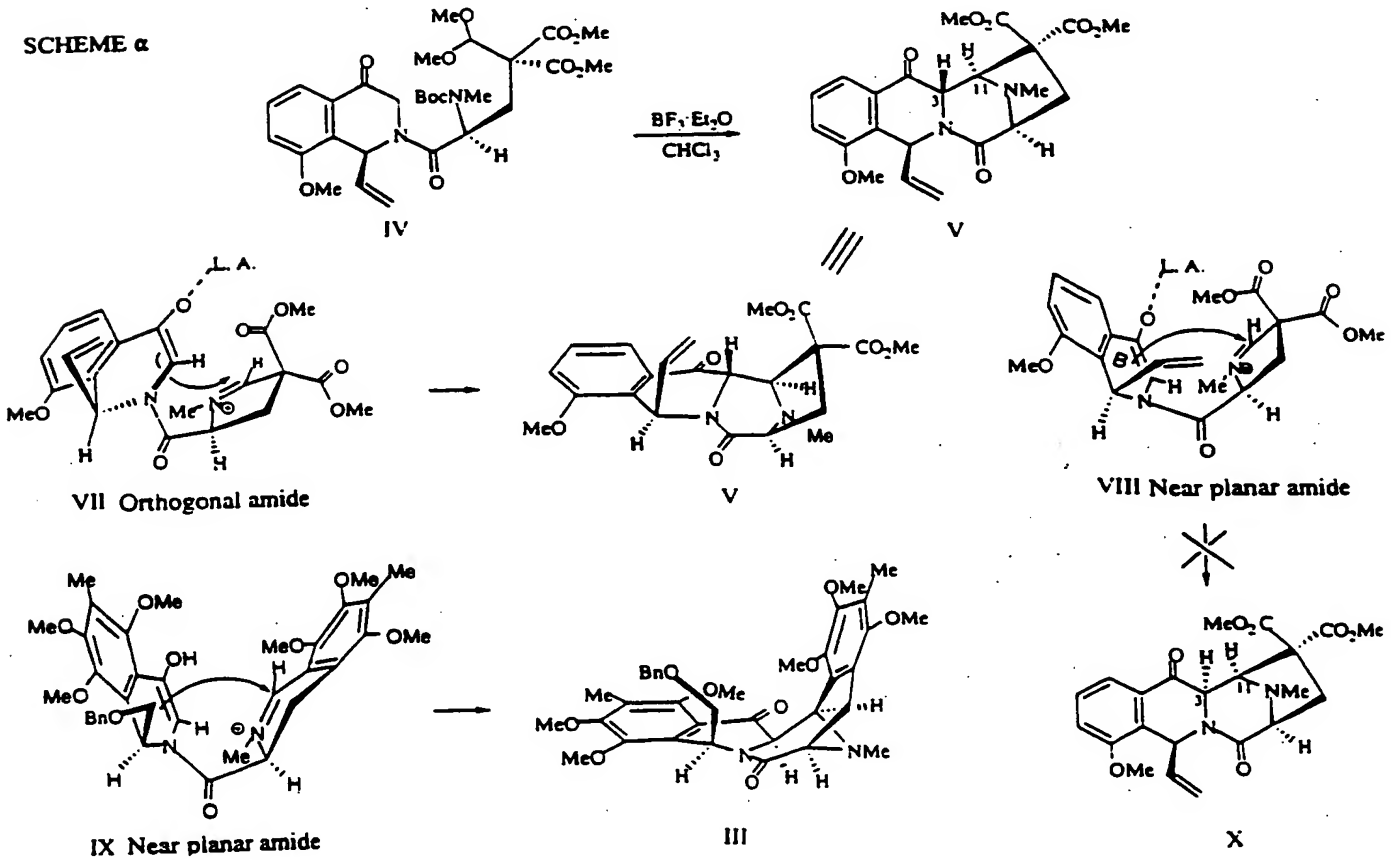
93

^{1}H NMR ($CDCl_3$, 400 MHz) 7.20-6.80 (m, 5H), 6.63 (s, 1H), 6.28 (t, J = 3.6 Hz, 1H), 5.17 (s, 1H), 4.46 (s, 1H), 4.20-3.60 (m, 18H), 3.15 (m, 1H), 2.80 (d, J = 17.3 Hz, 1H), 2.38 (s, 3H), 2.21 (s, 3H), 2.18 (s, 3H); MS (ESI +) *m/z* 616.8.

Discussion

Referring to Scheme α, below, there is a strikingly different outcome in the seemingly similar ring closure steps of **IV** to **V** and **39** to **40** (or **III**). We focus on the hypothetical iminium ions **VII** and **IX** which presumably appear in the two progressions. In each case, the system has been programmed such that attack of the nucleophile can only occur from one face of the iminium electrophile (β-as drawn). The interesting issue arises with respect to the stereochemistry of the reaction of the nucleophile. If the enol is attacked from its α-face, the "anti" backbone will be produced (cf. **IV** to **V**). Alternatively, attack from the β-face of the enol would give rise to a syn backbone product (**39** to **40**).

SCHEME α



Aside from issues of steric hindrance, there is a potentially important stereoelectronic consideration. In modeling the closure reaction, it is seen that the coplanarity of the amide substituents can be maintained only if the enol is attacked from its β-face. By contrast, attack at the α-face of the enol seems to require rotation about the amide in the direction of orthogonalization. From this perspective the syn backbone cyclization product would be expected (see stereostructure **IX**, which leads to **40** (or **III**).

Comparable modeling reveals that in the case of hypothetical stereostructure **VIII**, which could also arise from **IV**, attack at the β-face of the enol, though favored from the perspective of maximal maintenance of amide coplanarity, would incur a serious steric interaction between ring B and the two carbon bridge. This hindrance would be compounded by a particularly close abutment between the β-disposed vinyl and carbomethoxy groups if cyclization leading to the hypothetical **X** were to ensue. Hence, **V** rather than **X** is produced. By contrast, in **IX**, where the 6-membered iminium ring contains two additional sp^2 centers, the steric problems arising from the emerging syn backbone bridged system are perhaps reduced. In summary, it is proposed that cyclization of **39** (by way of stereostructure **IX**) is governed by the stereoelectronic factor (maintenance of amide coplanarity), while cyclization of **IV** (by way of stereostructure **VII**), is dictated by an overriding steric hindrance effect, leads to **V**.

Subsequent studies revealed that the stereochemical outcome of the Mannich closure step is also a function of the substitution pattern on the aldehyde-containing aromatic ring that enters into the cyclization event.

This shows that the Mannich-like closure of **39** to **40** (**III**) directly provides the backbone stereochemistry required for the subject alkaloids, in contrast to the stereochemical outcome in a related, earlier case (**IV** to **V**).

Based on prior art, compounds which contain a two tetrahydroisoquinoline aromatic carbon nitrogen framework, such as saframycin B, saframycin A (13,14), saframycin S (15), ecteinascidin 729 (Et 729)(16), Et 743 and Phthalascidin (3) have consistently exhibited pharmacological, antibiotic, cytotoxic, antitumor, anti-tumorigenic and cellular anti-proliferative activity both *in vivo* and *in vitro*. Several publications reveal that compounds which possess a two tetrahydroisoquinoline aromatic carbon nitrogen framework can function as cytotoxic antitumor agents.(13,14,15, **16**, 3) Saframycins are also known for their antibiotic capabilities. (19) These cytotoxic antitumor agents have been shown to interact with DNA. (18,14) In similar core structured saframycins and ecteinacidins as the compounds of this invention, interactions occur between DNA and the core tetrahydroisoquinoline aromatic carbon nitrogen framework. (2,18,20) Compounds disclosed in this invention, based on chemical and structural similarities to pthalicidins, ecteinicidins and saframycins, are therefore capable of interacting with DNA as well as possessing antitumor, antibiotic, cytotoxic and cellular anti-proliferative activity both *in vivo* and *in vitro*.

The pharmacological, antitumor, anti-tumorigenic, cytotoxic and cellular anti-proliferative activity of the compounds disclosed here both in vivo and in vitro can be determined by using published test procedures.

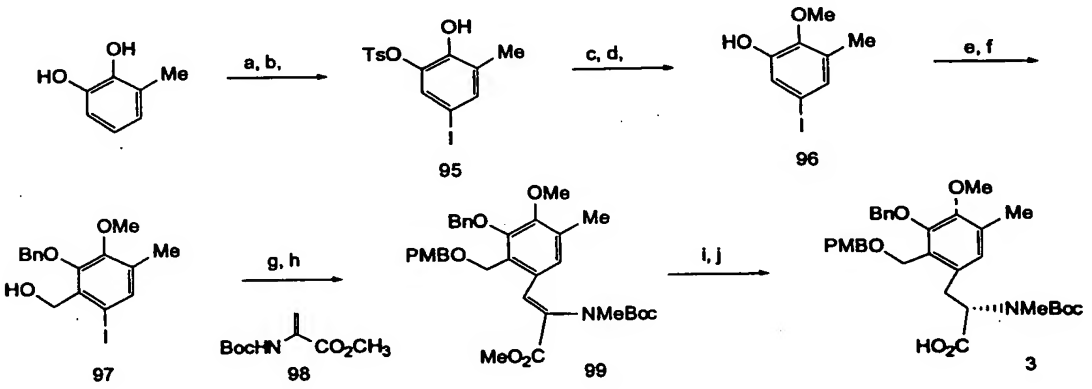
In vivo assays to determine a compound's antitumor capabilities

are typically performed in rodents or other species. Tumor growth is determined by the growth of tumors from transplanted transformed cells or tumor xenographs into or onto the animal. (See, eg., 13, 16, 21) *In vitro* assays to determine a compound's antitumor capabilities can be performed using a soft agar cloning assay to determine the *in vitro* effects of the disclosed compounds against primary tumor specimens taken directly from patients . (See, eg., 22) Anti-proliferative efficacy and cytotoxicity typically can be determined by absorbance of viable cells and the use of a reference wavelength to serve as an index for the viable cells . (See, eg., 3)

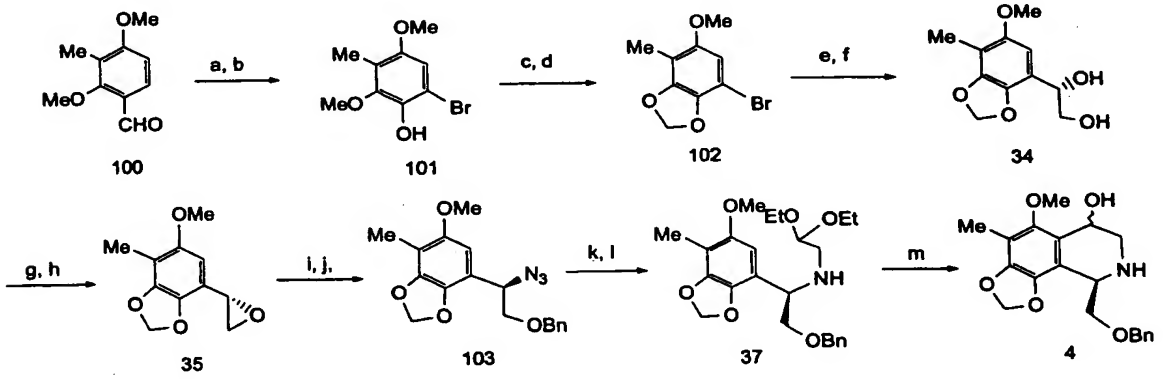
Example 10

Alternative construction of chiral subunits **3** and **4** for use in preparation of the Saframycin-Ecteinascidin Series.

The following schemes **12** and **13** result in subunits, **3** and **4**, which were used to prepare analogues within the Saframycin-Ecteinascidin Series.



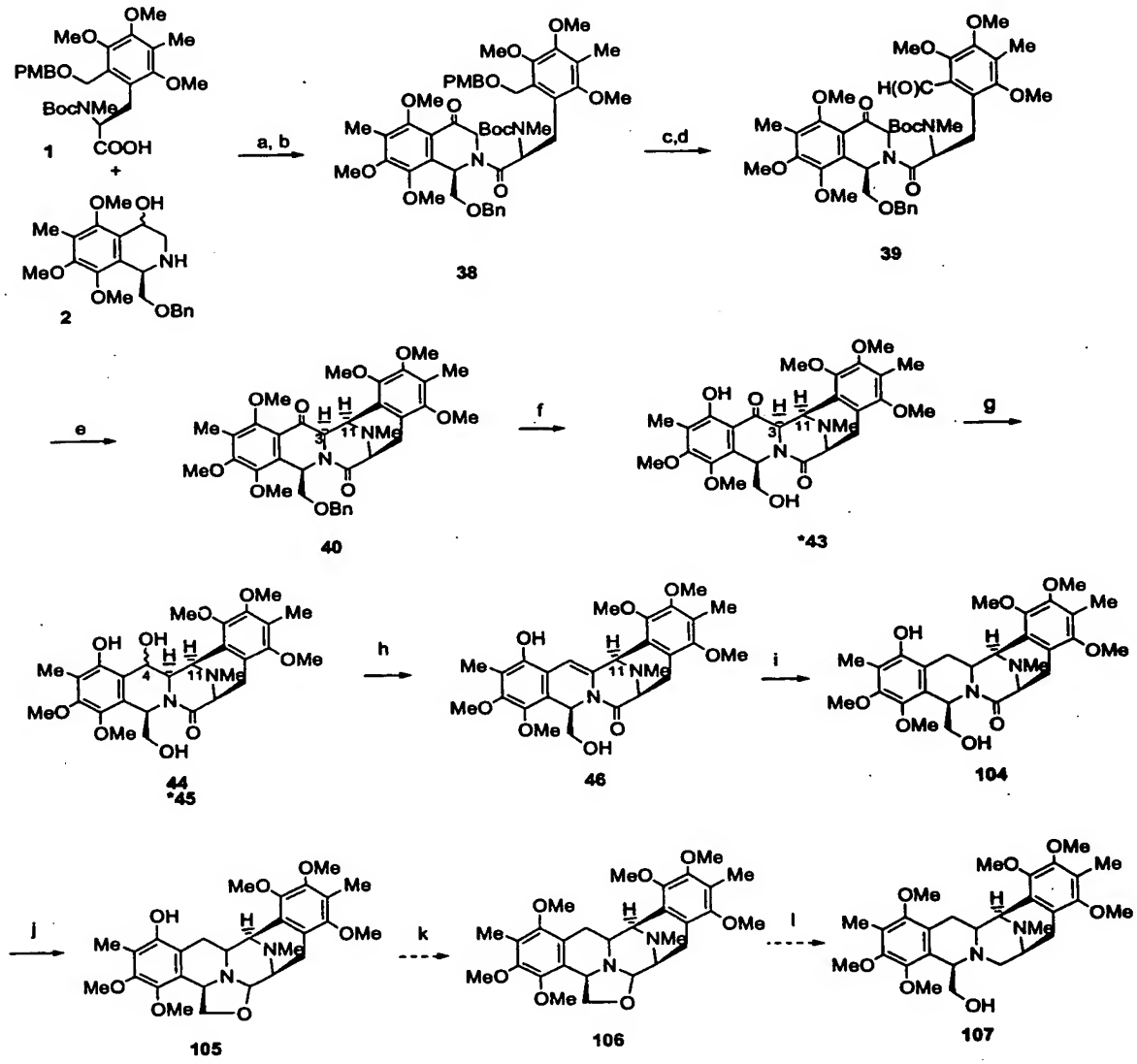
Scheme 12. a) TsCl, Et_3N, CH_2Cl_2, 0°C, 2 h, 93%; b) ICl, AcOH, 70°C, 20 h, 92%; c) CH_3I, K_2CO_3, acetone, reflux, 12 h, 100%; d) NaOH, EtOH, H_2O, reflux, 4 h, 94%; e) $(CH_2O)_n$, Me_2AlCl, CH_2Cl_2, 0°C->rt, 12 h, 77%; f) BnBr, K_2CO_3, acetone, reflux, 12 h, 95%; g) PMBCl, NaH, n-$Bu_4N^+I^-$, THF-DMF, rt, 12 h, 99%; h) 28, (*o*-tolyl)$_3$P, Et_3N, $Bu_4N^+Cl^-$, $Pd(OAc)_2$, DMF, 130°C, 12 h, 78%; i) (*S,S*)-Et-DuPhos, H_2 (100 psi), MeOH, rt, 2 d, 90%; j) NaH, MeI, THF, 0°C->rt, 12 h,60%.



Scheme 13. (a) *m*-CPBA, *p*-TsOH, CH_2Cl_2; then Et_3N, CH_2Cl_2-MeOH, 100%; (b) Br_2, K_2CO_3, CH_2Cl_2, -78°C, 80%; (c) $AlCl_3$, CH_2Cl_2, rt, overnight, 99%; (d) $BrCH_2Cl$, Cs_2CO_3, MeCN, reflux, 82%; (e) Vinyltributyltin, $Pd(PPh_3)_4$, toluene, reflux, 90%; (f) AD-mix-α, *t*-BuOH-H_2O(1:1), 0°C, 95%; (g) TsCl, pyridine-CH_2Cl_2; (h) K_2CO_3, MeOH, 72% for 2 steps; (i) NaN_3, $LiClO_4$, MeCN, 60°C; (j) BnBr,NaH, THF, 70% for 2 steps; (k) H_2, Pd/C, EtOAc, 90%; (l) K_2CO_3, $BrCH_2CH(OEt)_2$, MeCN, reflux, 72%; (m) 6N HCl, Dioxane, H_2O, then NaOH, 86% (β-OH:α-OH=2:3).

Example 11

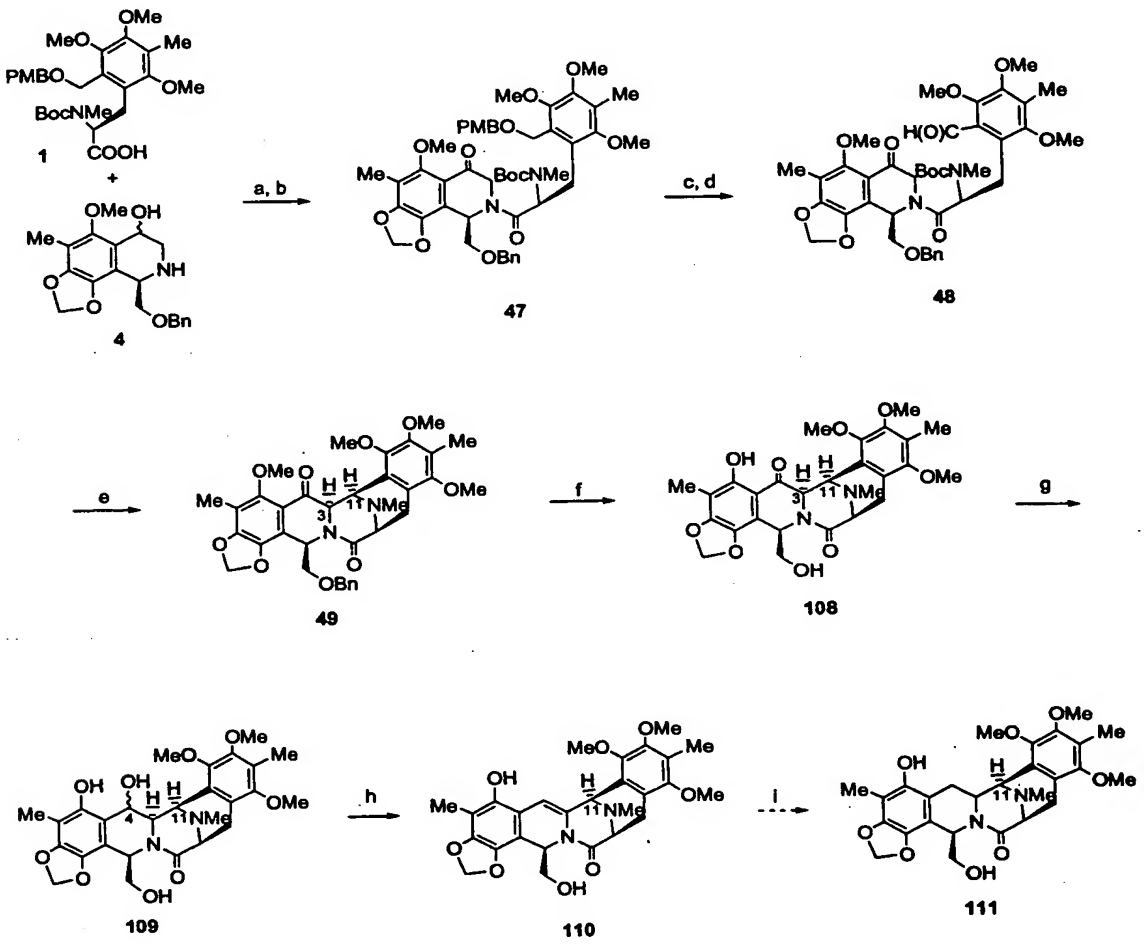
Synthesis of analogues within the Saframycin-Ecteinascidin Series using subunits **1** and **2** - Scheme 14.



Scheme 14. a) 1.1eq. BOPCl, 2.5eq. Et_3N, CH_2Cl_2, 10h, 63%; b) 1.5eq. Dess-Martin periodinane, CH_2Cl_2, 30min, 78%; c) 1.5eq. DDQ, CH_2Cl_2-buffer7.0-H_2O(20:1:1), 3h, 84%; d) 2eq. NMO, cat. TPAP, m.s. 4Å, CH_2Cl_2, 30min, 84%; e) formic acid, reflux, 1h, 70% f) BBr_3, CH_2Cl_2, 78°C, 85%; g) $NaBH_4$, MeOH, 0°C, 70%; h) CSA, Toluene, reflux, 1h, 70% ; i) H_2, 10%Pd/C, EtOH-EtOAc, Conc.HCl, 140psi, 75-85°C, 80%; j) $LiAlH_4$, MeOH; k) NaH, MeI, THF-DMF; l) EtOH, $NaBH_4$.

Example 12

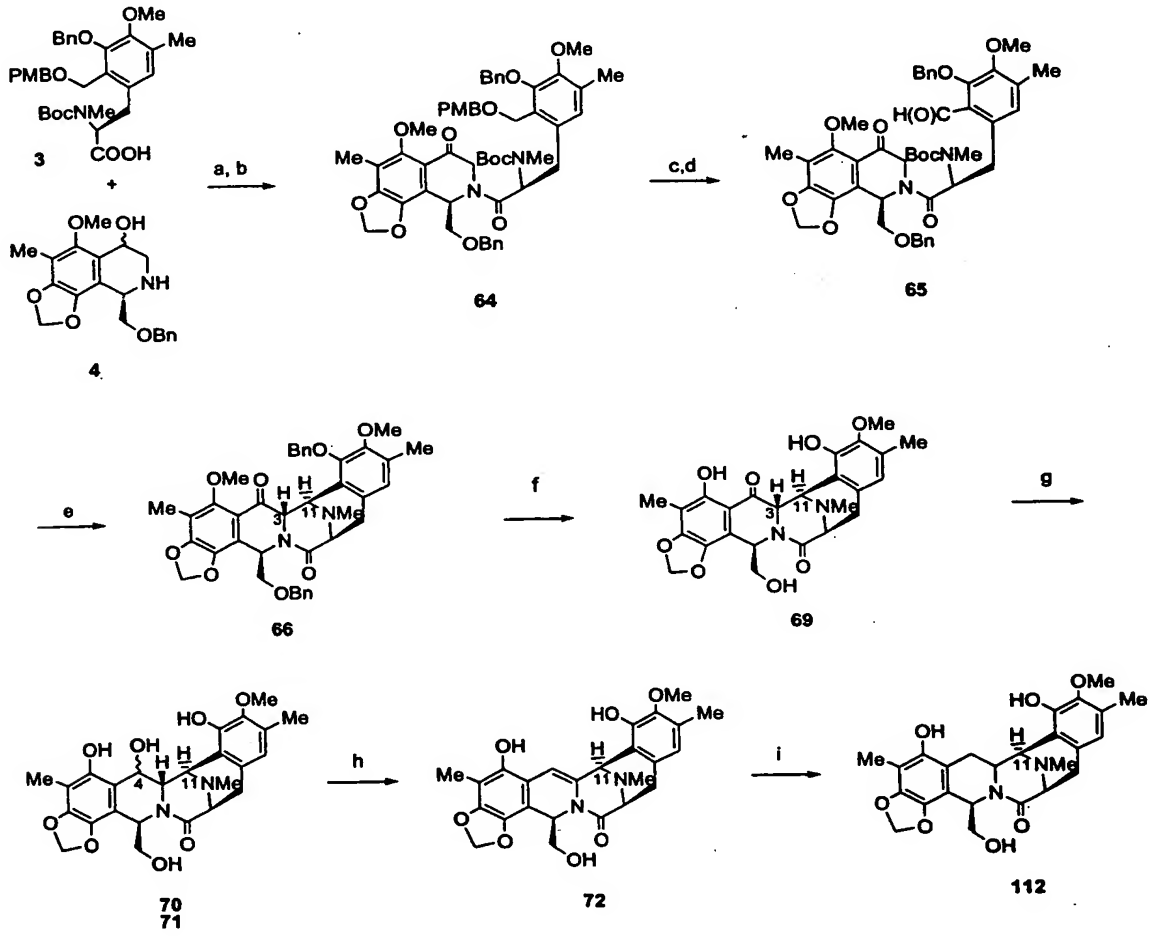
Synthesis of analogues within the Saframycin-Ecteinascidin Series using subunits **1** and **4** - Scheme 15



Scheme 15. a) 1.1eq. BOPCl, 2.5eq. Et_3N, CH_2Cl_2, 10h; b) 1.5eq. Dess-Martin periodinane, CH_2Cl_2, 30min, ~46% for 2 steps; c) 1.5eq. DDQ, CH_2Cl_2-buffer7.0-H_2O(20:1:1), 3h, 80%; d) 2eq. NMO, cat. TPAP, m.s. 4Å, CH_2Cl_2, 30min, 80%; e) formic acid, reflux, 1h, 60-70%; f) BBr_3, CH_2Cl_2, -78°C, 90%; g) $NaBH_4$, MeOH, 4h, 0°C, 70%; h) CSA, Toluene, reflux, 1h, 60%; i) H_2, 10%Pd/C, conc.HCl, EtOH-EtOAc, 14h, 75-85°C, 140psi.

Example 13

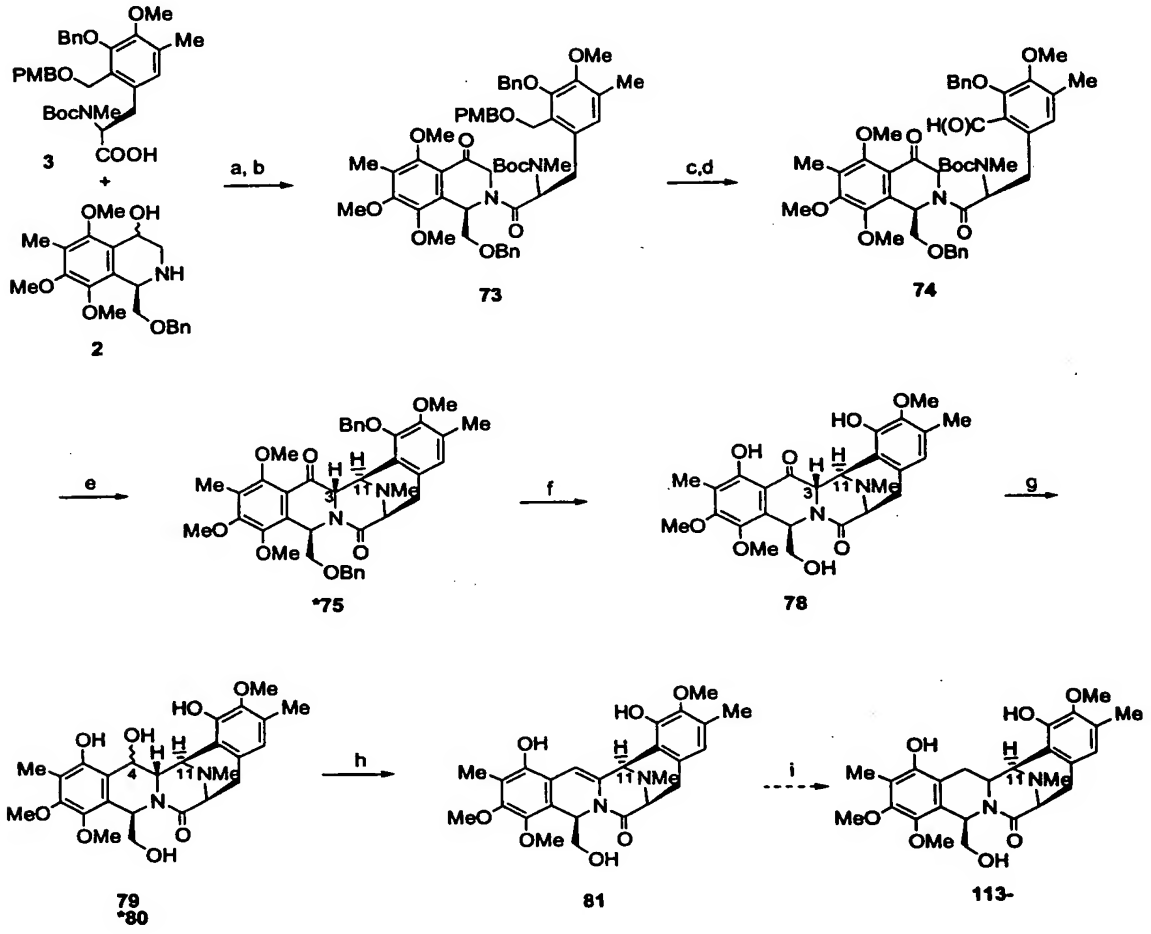
Synthesis of analogues within the Saframycin-Ecteinascidin Series using subunits **3** and **4** - Scheme 16.



Scheme 16. a) 1.1eq. BOPCl, 2.5eq. Et_3N, CH_2Cl_2, 10h; b) 1.5eq. Dess-Martin periodinane, CH_2Cl_2, 30min, 83% for 2 steps; c) 1.5eq. DDQ, CH_2Cl_2-buffer7.0-H_2O(20:1:1), 3h, 87%; d) 2eq. NMO, cat. TPAP, m.s. 4Å, CH_2Cl_2, 30min, 94%; e) formic acid, reflux, 1h, 60-70%; f) BBr_3, CH_2Cl_2, -78°C, 0.5h, 92%; g) $NaBH_4$, MeOH, 0°C; h) CSA, Toluene, reflux, 1h, >80% 2 steps; i) H_2, 10%Pd/C, EtOH-EtOAc, 1000psi, 75-85°C, 15h, 80%.

Example 14

Synthesis of analogues within the Saframycin-Ecteinascidin Series using subunits **3** and **4** - Scheme 17



Scheme 17. a) 1.1eq. BOPCl, 2.5eq. Et_3N, CH_2Cl_2, 10h; b) 1.5eq. Dess-Martin periodinane, CH_2Cl_2, 30min, ~50% for 2 steps; c) 1.5eq. DDQ, CH_2Cl_2-buffer7.0-H_2O (20:1:1), 3h, 70-80%; d) 2eq. NMO, cat. TPAP, m.s. 4Å, CH_2Cl_2, 30min, 70-80%; e) formic acid, reflux, 1h, 60-70%; f) BBr_3, CH_2Cl_2, -78°C 93-99%; g) $NaBH_4$, MeOH, 0°C, 50%; h) CSA, Toluene, reflux, 92%, i) H_2, 10%Pd/C, EtOH-EtOAc, 1000psi, 75-85°C, 15h.

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